THE BIOLOGY OF SENESCENCE

by
Alex Comfort



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To the question propounded . . ., I can make only one answer: yes, it is useful to prolong human life.

ILYA METCHNIKOFF (1907)

PREFACE

THIS book is a compilation. It was written as an aid to my own research, in a subject where it is difficult to know where to begin, but I hope that the references, at least, will be useful to others.

The denunciation of a subject and its current theoretical basis as 'unsatisfactory' is a relatively easy exercise—dealing with it satisfactorily is quite another matter. No biological treatment of senescence can hope to be satisfactory in the absence of a great deal of factual information which at present is not there. I have attempted to collect as much of this information as possible: since most of it comes from fields in which I have no experience, there are bound to be errors both of fact and of deduction in such a survey, and I hope that they will be pointed out to me.

I am deeply grateful to Professor Peter Medawar, F.R.S., under whom I have worked, to Professor J. B. S. Haldane, F.R.S., for kindly drawing my attention to a number of references I would not otherwise have seen, and to many colleagues whom I have molested for information or criticism, and whose help and advice has been invaluable, though they bear no responsibility for the result. I am also profoundly indebted to the Nuffield Foundation for several years' financial support, to Dr. Harrison Matthews, Director of the London Zoo, for access to its records, and to Miss Rosemary Birbeck for much help in preparing the manuscript and bibliography.

ALEX COMFORT

December 1954

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INTRODUCTORY AND HISTORICAL

MAN throughout history, and every individual since his childhood, has been aware that he himself, and those animals which he has kept in domestication, will undergo an adverse change with the passage of time. Their fertility, strength and activity decreases, and their liability to die from causes which, earlier in life, they could have resisted, increases.

This process of change is senescence, and senescence enters human experience through the fact that man exhibits it himself. This close involvement with human fears and aspirations may account for the very extensive metaphysical literature of ageing. It certainly accounts for the profound concern with which humanity has tended to regard the subject. To a great extent human history and psychology must always have been determined and moulded by the awareness that the life-span of any individual is determinate, and that the expectation of life tends to decrease with increasing age. The Oriental could say 'O King, live for ever!' in the knowledge that every personal tyranny has its term. Every child since the emergence of language has probably asked 'Why did that man die?' and has been told 'He died because he was old.'

Interesting psychological and historical speculation could be made on the part which this awareness has played in human affairs. From the biologist's standpoint, its main importance has been the bias which it has injected into the study of senescence. The child who asks the question, and receives the answer, is familiar with 'old' clothes and 'old' toys. He has always known that he, his pets, his cattle and his neighbours will become increasingly prone to breakdown and ultimate death the older they get. He has observed from the nursery that inanimate and

mechanical systems also deteriorate with the passage of time. He appears at a later age to derive some degree of comfort from the contemplation of the supposed generality, universality and fundamental inherence of ageing—or alternatively from drawing a contrast between Divine or cosmic permanence and his own transience. However inspiring this type of thinking may have been—and it features largely in the past artistic and philosophical productions of all cultures—its influence and its incorporation as second nature into the thought of biologists throughout history has seriously handicapped the attempt to understand what exactly takes place in senescence, which organisms exhibit it, and how far it is really analogous to processes of mechanical wear. One result of the involvement of senescence with philosophy and the 'things that matter' has been the prevalence of attempts to demonstrate general theories of senile change, including all metazoa and even inanimate objects, and having an edifying and a metaphysical cast. Prominent among these have been attempts to equate ageing with development, with the 'price' of multicellular existence, with hypothetical mechano-chemical changes in colloid systems, with the exhaustion induced by reproductive processes, and with various concepts tending to the philosophical contemplation of decline and death.

It is not unreasonable to point out that these theories have for the most part deeper psychological and anthropological [illegible]

a proximate cause of death in monocarpic plants, but the general concept, especially when it is made a universal, owes a large debt to the widespread belief in human cultures that sexuality 'has its price'. Extensions of mechanical analogies from the wearing out of tools to the wearing out of animal bodies are justifiable in a limited number of cases where structures such as teeth undergo demonstrable wear with use, and where this process limits the life of the organism; but they have also shown a tendency to become generalized in the hands of biologists who are devoted for philosophical, political or religious reasons, to mechanism in the interpretation of human behaviour. State-

ments that 'senescence is no more than the later stage of embryology' resemble Benjamin Rush's great discovery, that all disease is disordered function. They belong to the category of word-rearrangement games, which have long been played in those fields of study where there is as yet no 'hard news'.

Although the religious, poetic, metaphysical and philosophical literatures of senescence will not be examined here, the detection and examination of analogies based upon them, which have had a great, and generally adverse, influence on the [illegible] of the scientific method, and the first systematic English gerontologist,[1] provide one of the best critiques of the influence of such analogies and thought-patterns, and they will be quoted without scruple here.

The practical importance of work upon the biology of senescence, beyond the fundamental information which such work might give about the mechanisms of cell differentiation and renewal, can best be seen from the diagrams at Fig. 1–3 and 7. The advance of public health has produced a conspicuous shift in the shape of the survival curve in man so far as the privileged countries are concerned, from the oblique to the rectangular form. This has been due almost entirely to a reduction in the mortality of the younger age groups—the human 'specific age' and the maximum life-span have not been appreciably altered. The medical importance of work on the nature of ageing lies at present less in the immediate prospect of spectacular interference with the process of senescence than in the fact that unless we understand old age we cannot treat its diseases or palliate its unpleasantness. At present age-linked diseases are coming to account for well over half the major clinical material in any Western medical practice. The physician is constantly referring to the biologist for a scientific basis for geriatrics, and finding

[1] I dislike this word, but it is probably too well grown for eradication.

that it is not there. The amount of material on which such a foundation could be built has increased, though not very rapidly, during the present century. Its quantity is still inversely proportional *to the importance of the subject.*

There are not many adequate reviews of the modern biological literature. The most recent are those of Lansing (1951, 52). A previous review of mine contains little which is not repeated here (Comfort, 1954). Some of the more celebrated 'general theories' have received spirited treatment in a review by Medawar (1945). The literature of animal population statistics has been reviewed by Deevey (1947) and that of invertebrate senescence by Szabó (1935) and by Harms (1949). It is a pleasure to acknowledge my indebtedness to these reviews and to the bibliography of Shock (1951). A great deal of clinico-pathological material upon the age-incidence of various human diseases and the weights of organs throughout life has been collected by Bürger (1954). In a depressingly large number of fields, there has been little new information in the last twenty years. Other reviews of specific topics will be cited in their place. The senescence of plants is not discussed here: it has been reviewed in some detail by Crocker (1939), to whose paper there seems little to add.

Senescence is probably best regarded as a general title for the group of effects which, in various phyla, lead to a decreasing expectation of life with increasing age. It is not, in this sense, a *'fundamental', 'inherent', or otherwise generalizable process,* and attempts to find one underlying cellular property which explains all instances of such a change are probably misplaced. It is important and desirable to recognize the origins of many such general theories, which owe much to folk-lore on one hand and to the emotional make-up of their authors on the other. The demoralizing effect of the subject of senescence, even upon biologists of the highest competence and critical intelligence, is well illustrated by the following passage from Pearl (1928), the father of animal actuarial studies:

'*(Somatic death in metazoa) is simply the price they pay for* the privilege of enjoying those higher specializations of structure and function which have been added on as a sideline to the

main business of living things, which is to pass on in unbroken continuity the never-dimmed fire of life itself.'

Warthin (1929), whose insistence upon the fundamental impossibility of modifying the tempo of human ageing, now or at any time in the future, has an orgiastic tone quite out of keeping with the rashness of such a prediction, writes:

'We live but to create a new machine of a little later model than our own, a new life-machine that in some ineffable way can help along the great process of evolution of the species somehow more efficiently than we could do were we immortal. The Universe, by its very nature, demands mortality for the individual if the life of the species is to attain immortality through the ability to cope with the changing environment of successive ages. . . . It is evident that *involution* is a biologic entity equally important with *evolution* in the broad scheme of the immortal process of life. Its processes are as *physiologic* as those of growth. It is therefore inherent in the cell itself, an intrinsic, inherited quality of the germ plasm and no slur or stigma of *pathologic* should be cast upon this process. What its exact chemicophysical mechanism is will be known only when [illegible]

action by the moment of fertilization, and is dependent upon the potential fulfillment of function by the organism. The immortality of the germ plasm rests upon the renewal of this energy charge from generation to generation.'

This passage is highly typical of the literature of old age to the present day. There can be few branches of biology in which uplifting generalization of this kind has so long been treated as a respectable currency for scientific thought.

In general, the more elaborate the attempts to depict senescence in overall mathematical terms, the more intellectually disastrous they have proved. One of the most celebrated incursions of metaphysics into biology, that which postulates a separate 'biological time', is best expounded in the words of its sponsor, Lecomte du Noüy (1936):

'When we refer to sidereal time as being the canvas on which the pattern of our existence is spread, we notice that the time needed to effectuate a certain unit of physiological work of repair is about four times greater at fifty than at ten years of age. Everything, therefore, occurs as if sidereal time flowed four times faster for a man of fifty than for a child of ten. It is evident, on the other hand, that from a psychological point of view many more things happen to a child in a year than to an old man. The year therefore seems much longer to the child. . . . Thus we find that when we take physiological time as a unit of comparison, physical time no longer flows uniformly. This affirmation revolts one if the words are taken in a literal sense. But . . . the expression "flow of time" . . . is entirely false and does not correspond to a reality. When . . . we say that physical time measured by means of a unit borrowed from our physiological time no longer flows uniformly, it simply means that it does not *seem* to flow uniformly . . . Must one consider this fact as the indication of a difference of magnitude between our short individual period and the immense periods of the universe? Must we see a proof of the existence of such periods? Who knows? All that we can say at present is that our crude language, lacking appropriate words, translate this knowledge into improper, inadequate expressions such as "There are two species of time" or "Physiological time does not flow uniformly like physical time" . . . We must not let ourselves be duped by these words, etc. . . .'

It is startling how many distinguished biologists have subsequently quoted the notion of a distinct 'biological' time with apparent sanction. The alcoholic who draws on his bottle irregularly will find that its progress towards emptiness follows an irregular scale, 'alcoholic time', so that judged by the rate of emptying of the bottle, 'sidereal' time appears to progress unevenly. But variation in rate is hardly an occult, or even an unfamiliar, phenomenon. Like others before him, du Noüy has gone down clutching a platitude and come up embracing a metaphysical system.

In almost any other important biological field than that of senescence, it is possible to present the main theories historic-

ally, and to show a steady progression from a large number of speculative, to one or two highly probable, main hypotheses. In the case of senescence this cannot profitably be done. The general theories of its nature and cause which have been put forward from the time of Aristotle to the present day have fallen into a number of overall groups, and have been divided almost equally between fundamentalist theories which explain all senescence, or treat it as an inherent property of living matter or of metazoan cells, and epiphenomenalist theories which relate it to particular physiological systems or conditions. They are also fairly evenly divided between the various categories of Baconian idola. It is a striking feature of these theories that they show little or no historical development; they can much more readily be summarized as a catalogue than as a process of developing scientific awareness. To the fundamentalist group belong, in the first place, all theories which assume the existence of cellular 'wear and tear' (*Abnutzungstheorie*) without further particularization (Weismann, 1882; Pearl, 1928; Warthin, 1929); the mechanochemical deterioration of cell colloids (Bauer, Bergauer, 1924; Růžická, 1924; 1929; Dhar, 1932; Lepeschkin, 1931; Szabó, 1931; Marinesco, 1934; Kopaczewski, 1938; Georgiana, 1949); and pathological or histological elaborations of these, which attribute senescence to inherent changes in specified tissues, nervous (Muhlmann, 1900, 1910, 1914, 1927; Ribbert, 1908; Vogt and Vogt, 1946; Bab, 1948), endocrine (Lorand, 1904; Gley, 1922; Dunn, 1946; Findley, 1949; to cite only a few from an enormous literature in which the endocrine nature of mammalian senescence is discussed, stated or assumed), vascular (Demange, 1886), or even connective (Bogomolets, 1947). To the epiphenomenalist group belong toxic theories based on products of intestinal bacteria (Metchnikoff, 1904, 1907; Lorand, 1929; Metalnikov, 1937), accumulation of 'metaplasm' or of metabolites (Kassowitz, 1899; Jickeli, 1902; Montgomery, 1906; Muhlmann, 1910; Molisch, 1938; Heilbrunn, 1943; Lansing, 1942; etc.), the action of gravity (Darányi, 1930), the accumulation of heavy water (Hakh and Westling, 1934) and the deleterious effect of cosmic rays (Kunze, 1933). There are also general developmental theories which stress the continuity of senescence with

morphogenesis (Baer, 1864; Cholodkowsky, 1882; Roux, 1881; Delage, 1903; Warthin, 1929) or the operation of an Aristotelean entelechy (Driesch, 1941; Bürger, 1954), metabolic theories introducing the concept of a fixed-quantity reaction or of a rate/quantity relationship in determining longevity (Rubner, 1908; Loeb, 1908; Pearl, 1928; Robertson, 1923), attainment of a critical volume-surface relationship (Muhlmann, 1910 etc.), depletive theories relating senescence to reproduction (Orton, 1929) and finally an important group of theories which relate senescence to the cessation of somatic growth (Minot, 1908; Carrel and Ebeling, 1921; Brody, 1924; Bidder, 1932; Lansing, 1947, 1951). Most of the older theories have been reviewed, against a background of Drieschian neovitalism, in the textbook of Bürger (1954).

The distribution of dates in this catalogue sufficiently indicates the state of the subject. When Francis Bacon examined the relationship between animal specific longevity, growth-rate, size and gestation period, he concluded that the available facts were unfortunately insufficient to support a general theory. That conclusion remains valid in practically all the instances quoted, but Bacon's self-denial failed to set a precedent for his successors. Almost all these theories, judging from the literature, continue at some point to influence biological thinking: some can be partially, or even largely, justified by the suitable selection of instances. Others did not bear critical inspection at the time they were first formulated, bearing in mind the known behaviour of cells, and the known discrepancies in longevity and in rate of ageing between animals of similar size, histological complexity, and physiological organization. Relatively few are supported by any body of fundamental experiment. The devising of general theories of senescence has employed able men, chiefly in their spare time from laboratory research, for many years. It seems reasonable to assume that almost all the mechanisms which might theoretically be involved have been considered, and if we are to understand what does in fact occur in a given ageing organism, we now need a combination of general observation with planned causal analysis in experimental animals.

The main theories of ageing will be discussed in the text.

There are, however, a few which should be outlined in greater detail here—either because they are still of importance, or because, though untenable, they have a considerable surviving influence.

The most influential nineteenth-century contribution to this second category was probably that of Weismann, whose theory sprang directly from his distinction between germ plasm and soma. Weismann regarded senescence as an inherent property of metazoa, though not of living matter, since he failed to find it in protozoans and other unicellular organisms. Its evolution had gone hand in hand with the evolution of the soma as a distinct entity, and it was the product of natural selection, arising like other mutants by chance, but perpetuated as a positively beneficial adaptation, because 'unlimited duration of life of the individual would be a senseless luxury'. 'Death', according to this view, 'takes place because a worn-out tissue cannot forever renew itself. . . . Worn-out individuals are not only valueless to the species, but they are even harmful, for they take the place of those which are sound' (1882). This argument both assumes what it sets out to explain, that the survival value of an individual decreases with increasing age, and denies its own premise, by suggesting that worn-out individuals threaten the

undergo irreversible senescence was challenged early in the century by the studies of Child (1915) upon planarians, and of Carrel (1912) upon tissue culture. The assumption that all higher metazoa must *ex hypothesi* exhibit senescence, however,

fact that an inverse relationship exists between length of life and 'rate of living'. On the basis of calorimetric experiments, Rubner (1908, 1909) calculated that the amount of energy required for the doubling of weight by body growth was approximately equal in a number of mammals. The energy

requirement for the maintenance of metabolism, per unit adult body weight, was also approximately equal between species. Rubner inferred that senescence might, from these energy relationships, represent the completion of one particular system of chemical reactions, depending on a fixed total energy expenditure. He was obliged to erect a special category for man, whose energy requirement was found to be far higher than in laboratory or domestic animals. Loeb (1902, 1908) attempted to find out whether the temperature coefficient of this hypothetical reaction was identical with that of general rate of development. Working with echinoderm eggs at various temperatures, and using a hatchability criterion to determine 'senescence', if the word can be used in such a highly-specialized instance, he concluded that the two coefficients were distinct. The importance of this work has been that its presuppositions have recurred in later studies, where some authors have based very similar inferences about the relationship of growth and senescence to a 'monomolecular, autocatalytic reaction' on the shape and supposed mathematical proportions of the growth curve. As d'Arcy Thompson pointed out, this might equally prove the 'autocatalytic' character of growth in a human population. In fact, with suitable adjustment, curves based on biological material can be made to provide support for almost any hypothesis of this kind.

Little need be said of the various *toxic or pathological* theories of mammalian senescence. We are really left with five historically important theories, or groups of observations: the suggestion of Weismann that senescence is evolved, not intrinsic in all cellular matter; the work of Pearl (1928) which leads to the conception of a 'rate of living', such that factors which retard development or reduce metabolism tend in many organisms to prevent or postpone senescence; the work of Minot (1913, 1908), of which the most important surviving parts are his relation of senescence to the decline of growth, and his insistence upon its continuous and gradual character and its continuity with morphogenesis; the experimental studies of Child (1915), which showed that cellular differentiation and 'senescence' in planarians is reversible, and of Carrel (1912), who demonstrated that some tissue cells derived from adult animals

could be propagated indefinitely *in vitro*, and finally the theories of Bidder (1932).

Minot considered that senescence was the direct outcome of cell differentiation, that differentiated cells, by reason of the changes undergone, chiefly by their cytoplasm, in the course of morphogenesis, had become largely incapable of growth or repair. He believed that the negative acceleration of specific growth, found in a very wide variety of organisms, and ultimate senescence, were products of this process, and that the first was a measure of the second. It followed from this that the rate of senescence, so defined, mu [illegible] life and in infancy, when [illegible] Many of Minot's concept [illegible] cell differentiation, echoe [illegible] capacity of differentiated cells for growth, and the necessarily increasing liability to senescence of successive cell-generations, are now disproved or at least impugned. His work, however, leaves with us the two important concepts of a gradual process [illegible]

senescence, Minot arrived at the conclusion that the rate of senescence is highest in foetal, and least in adult, life. This concept has been widely adopted. Its validity depends upon the acceptance of Minot's definition; if senescence be regarded, as we shall regard it, in terms of deteriorative change in the organism's power of resistance, the idea requires qualification.

A far more important question, which had been latent in the literature since Ray Lankester (1870) pointed to the apparent non-senescence of fish, was raised by Bidder (1932). With the exception of Metchnikoff (1904, 1907) who was attempting to relate longevity to the form of the digestive tract, very nearly all biological theorists had assumed that senescence occurs in all vertebrates. This may in fact be so, but if it is not, then manifestly the general theories of senescence based on degree of tissue differentiation, irreplaceability of neurones, and other such systems fall to the ground. Bidder pointed out that there were several lower vertebrates in which there was no ground for suspecting that the mortality ever increased with increasing

age, beyond the inevitable increment from accumulation of evident injuries. He suggested that vertebrate *senescence is a correlate of the evolution of determinate growth and of a final absolute size.* Bidder regarded determinate size as a property which had evolved as a result of the migration of vertebrates to dry land. He pointed to a number of instances in fish where constant expectation of life, capacity for growth, and general vigour appeared to persist indefinitely (Bidder 1925). Bidder's argument is of importance, and is worth quoting in full.

'Giant trees, cultures of chick cells and of *Paramecium*, measurements of plaice and of sponges, all indicate that indefinite grow this natural. Galileo proved it fatal to swiftly moving land animals, therefore swiftly moving mammals and birds were impossible until their ancestors had evolved a mechanism for maintaining specific size within an error not impairing adequate efficiency. Even without evidence of evergrowing organisms, [illegible] to specific s [illegible] earth or ai [illegible] zygotic impulse to cell division and cell increase. Specific size is probably most important to birds, with their aeroplane mechanics strictly enjoining conformity of scale to plan; but to men it is most noticeable in man. Only familiarity prevents marvel at the rarity of meeting a man more than 20 per cent taller or shorter than 5½ ft., or of discovering his remains in any place, or any race, or any epoch. Probably our erect posture enforces accurate proportions of length to weight, for running.

'Adequate efficiency could only be obtained by the evolution of some mechanism to stop natural growth so soon as specific size is reached. This mechanism may be called the regulator, avoiding the word "inhibitor" so as not to connote a physiological assumption. However ignorant we are of its nature, its action is traced in anthropometric statistics; a steady diminution in growth rate from a maximum at puberty to a vanishing-point in the twenties. That the regulat [illegible] division is ended in the heart of a hen.

'I have suggested that senescence is the result of the continued action of the regulator after growth is stopped. The regulator does efficiently all that concerns the welfare of the species. Man is within 2 cm. of the same height between 18 and 60, he gently rises 2 cm. between 20 and 27, and still more gently loses 1 cm. by 40 or thereabouts. If primitive man at 18 begat a son, the species had no more need of him by 37, when his son could hunt for food for the grandchildren. Therefore the dwindling of cartilage, muscle and nerve cell, which we call senescence, did not affect the survival of the species, the checking of growth had secured that by ensuring a perfect physique between 20 and 40. Effects of continued negative growth after 37 were of indifference to the race; probably no man ever reached 60 years old until language attained such importance in the equipment of the species that long experience became valuable in a man who could neither fight nor hunt. This negative growth is not the manifestation of a weakness inherent in protoplasm or characteristic of nucleated cells; it is the unimportant by-product of a regulating mechanism necessary to the survival of swiftly moving land animals, a mechanism evolved by selection and survival as have been evolved the jointing of mammalian limbs, and with similar perfection' (Bidder, 1932).

... of senescence as ... natural ... ere may be two categories of vertebrates—those whose life span is fixed as in mammals, and those whose life-span is not fixed. From the theoretical point of view the establishment of the truth or ... in the elucid- ... st all the ... rom the ... demonstration that it is not universally present in vertebrates. ...

Bidder's theory marks the last major attempt to ... hypothesis of vertebrate senescence. No significant theory of

the general biology of ageing has appeared since, although its evolutionary basis has been discussed (Haldane, 1941; Medawar, 1952). The decline in abstract speculation about old age is probably in itself a very good augury for research. Much of the previous published matter abundantly justified the view of Bacon that 'the method of discovery and proof whereby the most general principles are first established, and then intermediate axioms are tried and proved by them, is the parent of error and the curse of all science'.

In later work, the relation between growth-cessation and ageing has been generalized to cover the senescence of all kinds of organisms which have a fixed life span, such as the rotifers (Lansing, 1947a) in which the mechanism of ageing may be, and very probably is, quite unlike that which occurs in vertebrates. The real importance of Bidder's suggestions lies, however, in the possibility they indicate that mammalian senescence may be a close evolutionary correlate of certain investigable mechanisms, such as homoeothermy, which have evolved with it. The probing of this possibility belongs to the future.

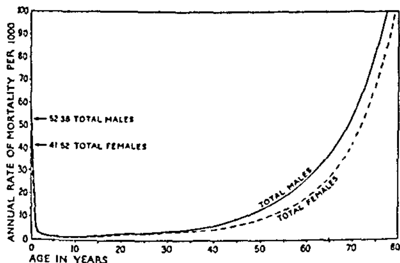


Fig. 1.—Annual rate of mortality per 1,000 by sex: United States, 1939–41.

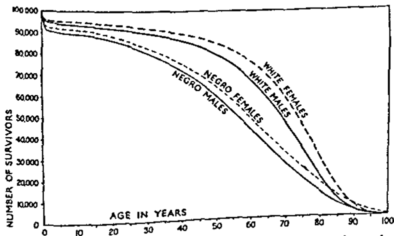


Fig. 2.—Number of survivors out of 100,000 born alive, for each race by sex: United States, 1939–41.

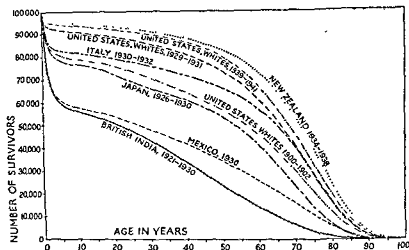


FIG. 3.—Number of Survivors out of 100,000 male live births, from recent life-tables for selected countries.



FIG. 4.—Frequency distribution of ages at death in a cohort starting with 100,000 live births, based on the mortality of white males: United States, 1939–41.

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THE NATURE AND CRITERIA OF SENESCENCE

1·1 *Measurement of Senescence*

SENESCENCE is a deteriorative process. What is being measured, when we measure it, is a decrease in viability and an increase in vulnerability. Other definitions are possible, but they tend to ignore the *raison d'être* of human and scientific concern with age processes. Senescence shows itself as an increasing probability of death with increasing chronological age: the study of senescence is the study of the group of processes, different in different organisms, which lead to this increase in vulnerability.

The probability that an individual organism which has survived to time x will die before time $x + 1$ depends on the *rate of mortality* (q) per 1000, meaning the number, out of 1000 individuals living at time x, who have died by time $x + 1$. The *force of mortality* (μ) is given at any age x by

$$\mu_x = -n^{-1}\frac{dn}{dx} = \frac{-d}{dx}\ln.n$$

where n is the number of individuals which have survived to age x.

In most organisms, the likelihood of dying within a given period undergoes fluctuations, often large, throughout the life cycle. Senescence appears as a progressive increase throughout life, or after a given stadium, in the likelihood that a given individual will die, during the next succeeding unit of time, from randomly-distributed causes; the pressure of the environment, which it has successfully withstood in the past, it now ceases to be able to withstand, even though that pressure is not increased. It is rare that we can determine the vulnerability of

an individual. Our estimate of it is determined statistically, upon a population. The demonstration of such an increase in vulnerability is a necessary condition for demonstrating senescence: it is, obviously, only a sufficient condition if selective mortality from age-distributed external causes is ruled out. Real populations are subject to mortality both from random and from age-distributed causes—the variation of exposure rate throughout life is familiar in man; grown men are subject to risks which do not affect children, and so on. Differences in 'risk' throughout life have been studied in some other animals, such as the locusts whose causes of death were analysed by Bodenheimer (1938) or the gall-fly *Urophora* (Varley, 1947). Pearson (1895), in his mathematical analysis of the curve of human survivorship into five components, attempted to limit the meaning of 'senile mortality' to one such component, reaching its maximum incidence between 70 and 75 years of age. This would be an ideal solution if it were practicable, but Pearson's analysis is artificial in the extreme, and his 'five separate Deaths' directing their fire at different age groups are not biologically identifiable. In general, however, a progressively increasing *force of mortality* and decreasing expectation of life in a population, if significant variation in exposure rate can be excluded, is evidence of the senescence of its individual members. The preliminary test for senescence in an animal species depends, therefore, on the life-table of an adequate population sample, studied with suitable precautions against selective causes of death.

The expected differences in behaviour, and form of life-table, between populations which age and which do not age are shown in Figs. 5*a*,*b*. In a population not subject to senescence and exposed only to random overall mortality, the decline of numbers is logarithmic, and animals die, *ex hypothesi*, from causes which would have killed them at any age. In a population exposed only to death from reduced resistance, due to senescence, the curve approaches a rectangular form: after a certain age, animals die from causes which would not have killed them in youth. In one case the force of mortality is constant, in the second it rises steadily with age. Thus in rats the force of mortality rises after the ninth month of life in a geo-

metrical progression (Wiesner and Sheard, 1934). Real survival graphs are commonly intermediate in form between the two ideal contours. Pearl and Miner (1935) distinguished three [illegible]

acteristic of populations which show no senescence, or which die out before it can become evident (Fig. 6). A fourth theoretical type, in which the curve is rectangular but inverse to that

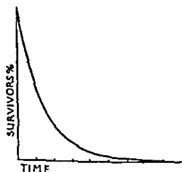


FIG. 5. (*a*)—Survival curve at a constant rate of mortality (50 per cent per unit time).

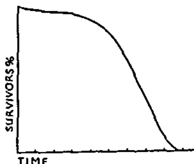


FIG. 5 (*b*).—Survival curve of a population which exhibits senescence.

found in the ideal senescent population, was recognized by Pearl (1940) as a theoretical possibility; it seems to be realized in nature among organisms which have a high infant mortality, but whose expectation of life increases over a long period with increasing age. This pattern of survival is characteristic of some trees (Szabó, 1931) but probably also occurs in animals. 'There may be animals in which the expectation of life increases continuously with age. This may be so for many fish under natural conditions. It certainly goes on increasing for a considerable time. Thus in a species where the expectation of life was equal to the age, or better, to the age plus one week, no members would live for ever, but a small fraction would live for a very [illegible]

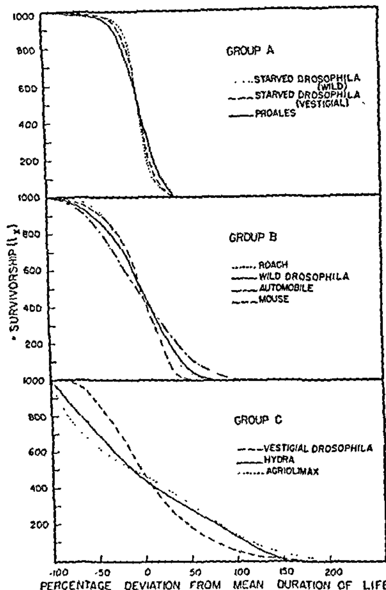


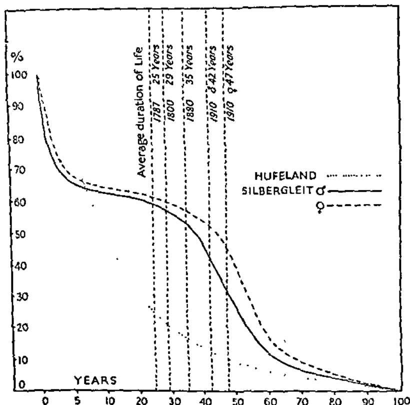
FIG. 6.—Types of survival curve (from Pearl, after Allee *et al.*, 1949).

Some real animal populations decline in an approximately logarithmic manner. The 'potential immortality' of individuals in a population following such a path of decline, an entirely meaningless phrase which has caused much philosophical agitation in the past, is not more significant as a practical issue than the 'potential' meeting of any pair of railway metals at infinity. No population of organisms which is subject to a constant overall death-rate contains 'potentially' immortal individuals. The only advantage which a non-senescent organism possesses over senescent forms is that the odds in favour of its death within a fixed period remain constant instead of shortening with the passage of time.

The human survival curve, in societies possessing developed medical services and a high standard of living, is intermediate between the rectangular and log-linear contours, but approaches the rectangular, with an initial decline due to infant mortality. Figs. 1–3 and 7 show, first, the comparative curves of mortality for populations in the present century living under different conditions of economic and climatic advantage, and second, the change in form of the life-table for North German populations between 1787 and 1800. Many life-tables for populations before the advent of scientific medicine are given by Dublin (1949). The significance of technical and economic privilege is nowhere more evident than in the study of life-tables. The effects of public health upon the life-table are expressed rather in making it approach more closely to the rectangular shape than in prolonging the preinflectional part of the rectangle. In very many organisms, and in man under bad social and medical conditions, the infant mortality is so large as to obscure all subsequent trends, the curve coming to imitate Pearl's fourth, inverse rectangular, type (Fig. 6). The terminal increase in liability to die may also be masked by cyclical variations in mortality associated with breeding or wintering, but the presence of such an increase remains an essential requisite for the demonstration of senescence in an organism. In many senescent populations, such as the sheep and cavies in Figs. 11 and 12, the survival curve in adult life is not so much rectangular as arith-linear, a constant *number* of individuals dying during each unit of time, the mortality necessarily decreasing as the supply

of animals decreases, like the companions of Odysseus of whom Polyphemus ate a fixed number daily.

The breakage rate of crockery or glasswear has sometimes been used to illustrate the decline of a non-senescent population (e.g. Medawar, 1952). A life-table for tumblers was actually



constructed by Brown and Flood (1947)—that for annealed tumblers approaches the curve of constant mortality, though only roughly, while the decline of a smaller group of toughened glass tumblers was nearly arith-linear (Fig. 8). Senescence, however, does apparently occur in tumblers, since abrasions of

the lip make subsequent cracking more likely (Brown and Flood, 1947).

It is convenient to treat survival curves such as those of man

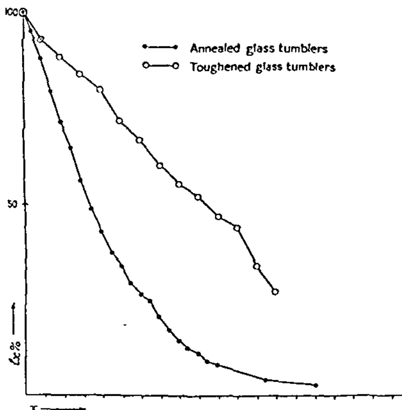


FIG. 8.—Survival curves for cafeteria tumblers.
A = 549 annealed glass tumblers ● — ●
B = 241 toughened glass tumblers ⊙ — ○
Time: 1 scale division = 2 weeks for Curve A, 5 weeks for curve B.
(Drawn from the data of Brown and Flood, 1947)

or *Drosophila* as combinations of the log-linear 'environmental' curve, found where the standing death-rate is high, with a terminal rectangular decline due to senescence, since it is evident that not all those individuals who die in middle life

owe any part of their misfortune to the senile increase in vulnerability, however early in life this is taken to begin.

Bodenheimer (1938) draws a useful distinction between the 'physiological' longevity of a species—that attained under optimal conditions in a genetically homogeneous population and approaching the longest recorded life-span within the species;

rectangular form, and this approximation is closest [illegible] some human societies. It is, however, pointless in terms of the actuarial definition of senescence to pursue a 'physiological' as opposed to a 'pathological' senescence in most laboratory animals. *If senescence is measured as increased* ***general*** *vulnerability, Bodenheimer's 'physiological' longevity represents only* the approximate region in which the rise in the curve of vulnerability to all assaults of the environment becomes so steep that even major protection against such assaults is insufficient to prolong life very greatly. The pattern can be modified and the apparent physiological longevity increased by removing specific causes of death—e.g. enteritis and ear disease in old rats (Korenchevsky, 1949) but the postponement of death obtainable in this way is itself limited, and argument about 'natural' death, apart from pathological processes, in mammals is quite otiose.

It is manifestly impossible to demonstrate senescence from life-tables unless the mortality in early and adult life is sufficiently low, and the number of animals reaching old age is therefore sufficiently high, for an endogenous increase in susceptibility to death-producing factors of random incidence to be evident. Thus wild mice die at a rate which precludes their reaching old age, but mice kept under laboratory conditions have a life-table similar to that of Western European human populations in the year 1900 (Leslie and Ranson, 1940, Fig. 30, p. 109 ; Haldane, 1953) : not even the most cherished labor-

atory population can receive as detailed medical attention as civilized man, but if such were possible, the life-table of mice might then approach that for Western European man in 1953.

[illegible]

proaching Bodenheimer's 'physiological' conditions.

Some of the limitations of the statistical definition of senescence have recently been re-stated by Medawar (1952). It is obvious that any survival curve can be simulated by judicious, or injudicious, choice of material. Tables based only on age at death, a single arbitrary event, are open to serious criticism if they are used as indices of a *continuous* process of declining vitality. The shape of such a curve is a measure of many things, including the genetic homogeneity of the sample. The incidence of various risks itself varies between age groups: the statistical appearance of senescence would, for example, be found in the life-table of any population of fish which was subject to frequent fishing with a net of fixed mesh size. Selective predation certainly produces effects of this kind of nature. The increased force of mortality among men of military age during a war is not a manifestation of senescence. On the other hand, some causes of mortality, such as cancer (Rutgers, 1953), have a curve of incidence which parallels the total curve of mortality. In employing the force of mortality as an index of senescence it is essential, as we have seen, to exclude so far as possible external factors which are not of random incidence in relation to age, yet this cannot be done with strict logical consistency. In the case of human life-tables, large secular changes in cause and incidence of death may occur within an individual life-span, while constitutional differences in rate of senescence between individuals ensure that the genetical composition of the survivors at, say, age 60, is not representative of the whole cohort under study. These sources of error are, in fact, capable of avoidance or correction for most practical purposes, but they must always be recognized in inferring senescence from any life-table.

Since there is no direct way of measuring the liability of an

individual to die without actually killing it, the statistical definition of senescence, although it reflects a real process in individuals, can only be tested upon a *population*.

It is evident that in applied biology, and especially in medicine, it is desirable to be able to infer not only the existence of senescence in a species but the degree of senile change in a given individual. This estimate must be based on secondary criteria, and can be made with accuracy only in forms whose life-cycle, like that of man or of *Drosophila*, has been subject to intensive study. The importance of the statistical definition of senescence is that it implies an obligatory recourse to adequate population studies. An over-common practice has been to keep a single specimen, a bird or a bullfrog, for ten or twenty years, and, when it is found dead, having been so for hours or possibly days, to describe histological appearances in its tissues in a note [illegible]

the force of mortality rises, neither can descriptions of 'senile' changes be properly based on single observations upon supposedly ageing organisms belonging to groups whose life-cycle, in relation to senescence, is not fully known.

In practice, other criteria than the life-table can be applied to organisms whose life-cycle is familiar, as secondary indices of senescence; these are distinct from mere measures of chronological age, based upon the morphology of scales, teeth or otoliths. Certain factors which are, in effect, direct measures of vigour or of vulnerability, such as the mortality from burns, (Ball and Squire, 1949), or even the annual absenteeism from sickness (Schlomka and Kersten, 1952) follow the general force of mortality in man. The supposed decline in the rate of wound healing proposed as a measure of senescence by du Noüy (1932) was based on grossly inadequate clinical material and is not supported by later work (Bourlière 1950). Less general criteria such as skin elasticity in man (Evans, Cowdry and Nielson, 1943; Kirk and Kvorning, 1949), organ weight and relative organ hyporplasia in rats (Korenchevsky, 1942; 1949), heart rate in Cladocerans (Ingle, Wood and Banta, 1937, Fig. 39, p. 146), milk yields in cattle (Brody, Ragsdale and Turner, 1923), egg production in fowls (Clark, 1940, Fig. 14, p. 63),

African Ibis
Night Heron
NUMBER SURVIVING
MONTHS
182
232

Fig. 9.—African Ibis [illegible]

NUMBER SURVIVING
DAYS
840

Fig. 10.—Orkney Vole (*Microtus orcadensis*). Survival of 24 individuals—sexes combined (London Zoo).

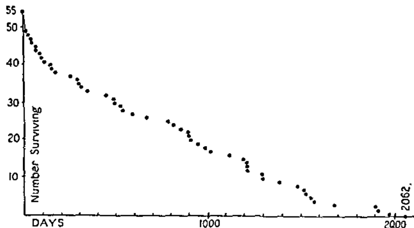
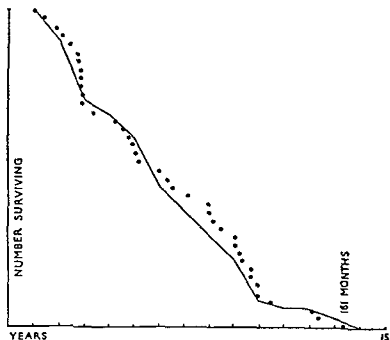


Fig. 11.—Patagonian Cavy (*Dolichotis patagona*). Survival of 55 individuals —sexes combined (London Zoo).

70
50
10
NUMBER SURVIVING
MONTHS
12 20 30
100
150
166

Fig. 12.—Mouflon Sheep (*Ovis musimon*). Survival of 77 individuals, beginning at 12 months—sexes combined (London Zoo).



[illegible]
Miss D. Gardner).

histological appearances of many kinds, and estimations of general or special metabolism are of value within sharply-defined limits, but all are subject to considerable variation apart from the general senile process. In retarded Cladocera, for example, where mean life-span is artificially prolonged by postponing growth, the heart rate fails to decline before death to the low levels normally found in old age (Ingle, Wood and Banta, 1937). Minot (1908), Hertwig and others considered that [illegible]

lation into more precise biochemical terms. Dehydration was also formerly regarded as a general senile phenomenon. From a recalculation of older data, however, and from fresh material,

Lowry and Hastings (1952) find that increased hydration, due perhaps to extracellular oedema, loss of cells, and even gross pathological causes such as heart failure, is the most consistent finding in senile mammalian tissue. There is at present no biochemical sign characteristic of 'oldness' in tissues or in cells, and the search for one may well reflect a fundamental misconception. It is in assessing the relevance of all such criteria to the main phenomenon of senescence, the decline in resistance to random stresses, that the statistical approach is essential. All assertions about senescence based upon pathological anatomy, or upon general theories which treat it as a single process, are open to question.

The *decline of growth rate* throughout life in some or all tissues appears to be a near-universal feature of metazoa.

'The specific growth rate always falls: living tissue progressively loses the power to reproduce itself at the rate at which it was formed. Minot arrived at this generalization, which should rightly be known as "Minot's Law", from the collation of his percentage growth-rate curves; and it was he who first recognized that the point of inflection of the integral curve of growth, and the division it makes between a period of positive and negative acceleration, is not of critical importance. The progressive dissipation of "growth energy" which this first law affirms was thought by Minot to be an expression of the phenomenon of senescence—"ageing" with its everyday implications. Senescence is not, in this view, a process which sets in after a preliminary period of maturation has run its course: senescence *is* development, looked at from the other end of life' (Medawar, 1945b).

The use of this criterion, which is a readily measurable one, and can be applied to smallish groups of animals with suitable precautions, as well as to single tissues or organs, implies the acceptance of Minot's definition of senescence. The definition is defensible. *On the other hand, one of the important points at issue at the present moment is precisely whether all animals* which show a decline in the specific growth rate—all verte-

as a result of some factor which also causes that decline. The decline is not a measure of senescence in its actuarial sense, since it does not run parallel with the force of mortality, and it would not be even an obligatory precursor of senescence if mortality only increased with age in those animals whose capacity for renewal or growth in some or all tissues has fallen to zero. It is with actuarial, deteriorative senescence that we are here concerned—if senility implied *only* the decline of growth rate in man, it would cause little public concern.

It is possible that future work will produce a workable and justifiable 'direct measure' of senescence in individuals, based on the time-lag in cell-division of tissue explants derived from old animals (Cohn and Murray, 1925; Suzuki, 1926; Medawar, 1940). No practical test of this kind has yet been developed, however—meanwhile the critical observations on the distribution of senescence in vertebrates have almost all to be made upon organisms (large fish, crocodiles, tortoises) where life-table studies are out of the question. In these forms it is relatively easy to observe histologically or by a mating test, the degree of reproductive power persisting in individuals of known age. Inferences based on 'reproductive' senescence are therefore easy to draw, compared with the insuperable difficulties involved in measuring the force of mortality in such cases.

Reproductive decline is a very general feature of those vertebrates which undergo senescence as judged by the increasing force of mortality: its evidences in various forms include gonadal changes, loss of secondary sexual characters, cessation of ovarian cycles, and a fall in sperm production, fertilizing power, hatchability, litter size and viability. These changes follow a time scale which is different from that of the increase in force of mortality, however, and which bears no constant relation to that increase in different species. The gonad often appears to behave as an 'organism' having its own determinate life-span, but this is equally true of other structures, such as the thymus. The limited life of the gonad is in a special category only because, in terms of evolutionary teleology, the gonad is the significant part of the organism. Ageing of the whole organism after a prolonged post-reproductive period is a process which is realized only by human interference, at least so far as most

species are concerned, and not 'envisaged' by evolutionary teleology. It could be argued that once gonadal senescence has become established in a species, eventual somatic senescence is a rule inevitable from the withdrawal in post-reproductive life of the selection-pressure towards homoeostasis. A clear physiological link between the activity of the gonad and the growth and survival of the animal has been demonstrated in a few forms (e.g. *Daphnia*, Edlén, 1937, 1938), although even in *Daphnia*, oogenesis continues until death (Schulze-Röbbecke 1951). In many vertebrates, however, even total castration has little or no adverse effect on longevity, and may increase it. Although senescence of the gonad is, in an evolutionary sense, the most important form of ageing, it is not self-evident that in the artificially-protected animal it must always be followed by generalized somatic senescence, unless the two processes are causally related. Such an identification reflects, once more, a human preoccupation. Reproductive function, because of its ease of measurement, remains at most a justifiable test of continuing vitality in old animals—fertility at least indicating the absence of irreversible organ changes in one important system.

Metabolic decline, either measured directly by calorimetry and manometry, or inferred from reduction in spontaneous activity, has also been regarded as an index of senescence—often on theoretical grounds, as representing the accumulation of inactive 'metaplasm' at the expense of active protoplasm (Kassowitz, 1899, etc.) or the completion of a 'monomolecular autocatalytic reaction' such as that postulated by Robertson (1923) or Bertalanffy (1941). The decline of heart rate in Cladocerans (Ingle, Wood and Banta, 1937) has already been mentioned. The mean resting heart rate in man also tends to decline throughout foetal and postnatal life. Child measured the age of hydromedusae by the decline in their rate of pulsation (Child, 1918). In some invertebrates (planarians, Child, 1915; hydromedusae, Child, 1918; molluscan adductor muscle, Hopkins, 1924, 1930) and in some isolated vertebrate tissues (articular cartilages, Rosenthal, Bowie and Wagoner, 1940, 1941, 1942; rat blood vessels, Lazovskaya, 1942, 1943; avian muscle, Glezina, 1939; rabbit muscle, Cheymol and Pelou, 1944; rat brain homogenate, Reiner, 1947; liver, kidney and heart homo-

genates, Pearce, 1936; mouse lymphoid tissue, Victor and Potter, 1935) O_2 uptake has been reported to decline with age. Calorimetric experiments on the whole mammal indicate a general decline in heat production with increasing age (Sondén and Tigerstedt, 1895; Benedict and Root, 1934; Magnus-Levy and Falk, 1899; Shock, 1942, 1948; Benedict, 1935; Boothby *et al.*, 1936; Kise and Ochi, 1934). This decline, however, like that of growth-energy, is greatest in early life, and relatively slight in man after the age of 50 (Shock, 1953). It does not parallel the senescent increase in mortality. There is also gross individual variation. Kunde and Norlund found (1927) no significant decrease in the basal metabolism of dogs up to 12 years of age. In rats, Benedict and Sherman (1937) found a slight decrease in heat production with increasing age, measured in the same individuals, but with the onset of senescence the body weight itself declined, so that the metabolism per unit body weight appeared to increase. In man O_2 uptake per litre intracellular fluid shows no decrease with age (Shock, Watkin and Yiengst, 1954). A fuller bibliography is given by Shock (1951, 1953). It is not so far possible, in most organisms, to base intelligible estimates of individual senescence upon changes in metabolic rate.

1·2 *Forms of senescence*

Increase in death-rate and decrease in resistance after a certain age might be expected in a number of model systems. The curve of failure rate for mechanical devices such as lamp bulbs, telephone switchboards (Kurtz and Winfrey, 1931), or radar units bears a superficial resemblance to the mortality curve of a senescent population, both in cases where all-or-none failure results from wear or from the passage of time (lamp filament failure, crystallization of metals, changes in condenser dielectrics) or where wear is cumulative and inefficiency increases to the point of failure (frictional wear, decline of cathode emission). The resemblance to biological senescence is closest in cases where several coincident processes ultimately become self-reinforcing. The 'death-rate' of motor-cars, plotted by Griffin (1928) and Pearl and Miner (1935) is closely similar to that of wild-type *Drosophila* (Fig. 6).

1·2·1 MECHANICAL SENESCENCE

A few precise analogies to the failure of a non-replaceable part in a mechanical system are known to occur in organisms. Deterioration of the waxy epicuticle in insect imagines and of the teeth in the African elephant (Perry, 1953), the mongoose (Pearson and Baldwin, 1953), the shrew (Pearson, 1945; Pruitt, 1954) and *some large carnivores* are

...malian kidney is an example of the incidental loss of essential structures, but one which rarely reaches the point of causing death *per se*. On the other hand, the differences between an old cart and an old horse are sufficiently striking to make the extensive acceptance of 'wear' as an explanation of senescence, and the resort to mechanical analogies based on the 'spontaneous slow decomposition' of explosives (Lepeschkin, 1931) or the behaviour of inanimate colloids (Růžická, 1924; Dhar, 1932) largely irrelevant. 'The old organism does not contain old colloids, it contains newly-formed colloids of an old character' (Lansing). The mean half-life of human protein is 80 days, of liver and serum proteins 10 days, and that of the carcase proteins 158 days (Bender, 1953). The continuation of high protein turnover in adult life has been demonstrated by isotope studies (Shemin and Rittenberg, 1944) though the turnover of materials such as collagen decreases almost to zero with increasing age (Perrone and Slack, 1952; Neuberger and Slack, 1953). The weakness of the 'colloidal' concept of ageing had been pointed out even before the discovery of colloids: 'Quoniam vero duplex est duratio corporum: altera in identitate simplici ...

A chemical extension of the idea of 'mechanical' senescence

[3] *Since there are in fact two ways in which bodies maintain their identity*, the first, which applies only to inanimate objects, is simply by remaining *the same*. The second which applies to *plants and animals*, is by renewing themselves; and they do this by means of nourishment.

could be based more plausibly on the existence of expendable enzyme systems renewable only by cell division, to explain the ultimate death of some fixed postmitotic cells (Cowdry, 1952); this concept will be discussed later on. In all organisms except those which are capable of total regeneration, mechanical injury of a more general kind must accumulate with time, but this process will vary greatly in rate under different environmental conditions. The constancy of the specific age in forms which senesce is a strong argument against the primacy of 'mechanical' ageing.

1·2 2 'ACCUMULATION' AND 'DEPLETION'

In addition to a limited number of cases in which mechanical wear normally, or potentially, terminates an animal life-cycle, most of the other postulated 'causes' of senescence such as the accumulation of metabolites (Metchnikoff, 1915; Jickeli, 1902) and the exhaustion of stored irreplenishable reserves, do very probably contribute to senescence in specific instances. The very large literature of calcium and pigment accumulation in the cells of higher animals (reviewed by Lansing, 1951) deals with changes which are probably reversible consequences, rather than primary causes, of an underlying senile process. Lansing (1942) found, however, that reduction in the calcium content of the medium greatly increased the life-span of rotifers. A similar increase was produced by a single immersion in weak citrate solution. Accumulation of calcium with age was demonstrated in the same organisms by microincineration. Similar processes are described in plants (Molisch, 1938; Ahrens, 1938; Lansing, 1942). The 'life' of spermatozoa, though by no means analogous, has been shown to be prolonged by chelating agents which bind Cu^{++} and Zn^{++} (Tyler, 1953). In the case of the rotifer, at least, the evidence for an accumulative element in senescence is fairly strong.

Depletion certainly terminates the life-cycle of some non-feeding insect imagines, especially among Lepidoptera (Norris, [illegible]

logical derangement caused by spawning (Orton, 1929). The

incidence of parental mortality in molluscs is reviewed by Pelseneer (1935). Attempts to explain the human menopause in terms of exhaustion of the supply of ova will be discussed later. There is no evidence of a 'depletive' senescence in mammals, unless the decline of growth rate be taken as evidence of the exhaustion of some hypothetical substance.

1·2·3 MORPHOGENETIC SENESCENCE

The accumulation of injuries presents no biological problem —it is readily observable in structures such as skin, and the only serious difficulty lies in assessing its contribution to ageing in particular structures or animal species.

But in addition to the processes of mechanical or metabolic senescence, and sometimes affecting the same organisms if they are protected from these, it is necessary to postulate a further, morphogenetic senescence to explain the sequence of events observed in many organisms. This senescence has been considered to arise directly from the operation of the processes of cell development which determine the shape and size characteristic of the species and of its organs either through changes in cell behaviour, or through the effects of divergent processes of heterogony; it expresses itself as a decline in the capacity to regenerate or maintain structures or conditions which, during growth and a post-growing period of variable duration, are normally regenerated and maintained. Morphogenetic senescence is a cumulative failure of homoeostasis, affecting the body as a whole, to which coincident or dependent mechanical failure or accumulative processes may contribute, but which appears to be continuous with the processes which control cell-differentiation and regulation. More accurately, it appears to represent the withdrawal of coordination between these processes, so that physiological homoeostasis 'falls apart'. It is this form of senescence which characterizes higher vertebrates and is particularly well seen in man. The chief evidence that this, morphogenetic, senescence is more that the 'sum of environmental insult' which was formerly invoked to explain it, is the existence in many organisms of specific age, analogous to specific size and possibly related to it, which displays little environmental, but marked inter-race and interspecific, variation.

Much information about the behaviour of self-restoring and self-regulating systems, and a number of important general concepts, are now available from the study of mechanical models. These analogies apply, strictly, only to the elucidation of single components of the process of maintaining physiological stability; the most important feature of 'cybernetics' and homoeostasis in the organism has no precise mechanical analogy. This is the fact that the homoeostatic process, the state of quantitative invariance, or self-restoration, in various physiological systems, is superimposed on qualitative and quantitative change in the nature of the systems themselves, their specificity, relative proportions, and function—in other words, upon developmental change. There is a strong inference that senescence occurs when these long-term changes, which are probably controlled or initiated largely by the same humoral mediators which function in day-to-day homoeostasis, pass out of control, or reach a point beyond which homoeostasis is no longer possible.

This argument ultimately stands or falls by the result of our study of the phylogeny of senescence. If mammalian senescence results from morphogenetic processes which ultimately escape from the homoeostatic mechanisms that operate during adult vigour, and if, on the other hand, some other vertebrates reach a state of growing, or self-replacing, equilibrium, even over limited periods, the problem of understanding mammalian senescence will be very greatly restricted in theoretical scope, though probably not very greatly simplified in experimental detail. Such an equilibrium would be most likely to be found in those forms where differential growth is least evident. The evidence on this point will be examined later.

1·3 *Senescence in Evolution*

Senescence has frequently been regarded as an evolved adaptation, rather than as an inherent property of somatic organization. This view, which is reasonably well in accord with the existing, and very incomplete, evidence of its distribution in phylogeny, was held by Weismann in spite of his insistence on the contrast between germinal immortality and somatic mortality. Weismann, however, regarded senile change,

and the limitation of the individual life-span, as a positively beneficial adaptation, and his argument is, as we have seen, of a circular kind.

The theoretical difficulties of devising a system in which *short* life is selected as a character of fitness are considerable though not insuperable.[1] In any circumstances where a high number of generations in unit time has an adaptive value, the Weismannian argument against individual longevity might hold. The most conspicuous adaptive modifications of life-span in phylogeny seem, however, to be chiefly in the other direction. The development of social insects probably depended upon the evolution of long-lived sexual forms, and it is very likely that a similar process may have operated in human phylogeny, in connection with the development of social behavio[illegible] family unit. Not only was the [illegible] long [illegible] lea[illegible] [illegible]ducence, but, with the dev[illegible] [illegible] power and social organization, the advantages of possessing the experience of even a few long-lived members was probably very high in any early hominid community. The social animals, especially man, provide one of the best examples where longevity depending on factors outside the reproductive period can theoretically be subject to positive selection in terms of fitness.

The chief objection to Weismann's idea of senescence as an adaptive effect is the rarity of its demonstrable occurrence in nature. In all but the few forms discussed on pp. 108–13, senescence is a *potentiality*, not a benefit or a handicap; it is realized only when we interfere artificially with the animal or its environment, and it is arguable whether evolution can select for such potentialities. Bidder, it will be recalled (p. 12), considered that senescence in mammals was an evolutionarily unimportant 'by-product' of an important positive adaptation, the limitation of size. It would indeed be possible to attribute senile change to the accumulation of such by-products outside the reproductive period. More recently it has been suggested that

[1] Ribbands (1953) found an apparent example in worker bees, where the summer brood could increase its working life by consuming pollen, but uses it instead to rear additional larvae.

senescence is to be regarded not as the positively beneficial character which Weismann believed it to be, but as a potentiality lying outside the part of the life cycle which is relevant to evolution. It has certainly been 'evolved', in that the living system which senesces has evolved, but it has not evolved as a physiological mechanism. The line of argument which appears most plausible is that suggested by Medawar (1945, 1952). It seems probable, for a number of reasons, that except in certain social animals there can be little effective selection pressure against senescence as such. Normal population structure in wild communities of animals, even in the absence of senescence, leads to a continual preponderance of young reproducing over old reproducing individuals, sufficient to override the advantage in number of progeny which arises from a longer reproductive life. Death from senescence is itself in many species so rare an event in the wild state that failure to senesce early, or at all, has little value from the point of view of survival. In many forms the *cessation or reduction of breeding capacity precedes senescence* proper—with certain exceptions in social animals, events occurring in the post-reproductive period are theoretically outside the reach of selection, and irrelevant to it. A consequence even more important than the mere failure of evolutionary processes to operate in favour of the postponement of senescence follows from the same facts. In view of the constant reproductive preponderance of young individuals, the postponement of the action of a harmful genetic effect until late in the reproductive life is almost equivalent, in selective value, to its complete elimination: the longer the postponement, the closer the equivalence. The evolutionary 'demon' is concerned only to clear the part of the life-span in which he works, not the parts which might be reached if the environment were artificially made more favourable. This mechanism, by acting to move all adverse genetic effects which are capable of postponement and all the consequences of divergent but temporarily beneficial systems into the late reproductive or post-reproductive life, may itself provide a partial explanation of the evolution of senescence, as Haldane (1941) has already suggested. The selective equilibrium reached in man would be expected in this case to be such that the force of mortality is lowest when reproductive

activity is potentially highest, though the observed lowest level falls rather earlier than this (10–12 years in males, Greville, 1946).

The selectionist argument which regards senescence as the decline of evolved survival-power through successive age groups is most convincing when we apply it to mammals and birds: among invertebrates, reservations require to be made. In those which are predominantly seasonal, with a total life-span less than one year, and which winter as fertilized adults, it is by no means true that at all times of the year young individuals must outnumber old in a free-running population. The autumn contingent of overwintering animals will consist of 'old' individuals. In such forms, the selective advantage of different genotypes will vary from season to season, and there will be an ultimate requirement that the adult be capable of living long enough to overwinter. Forms producing two broods annually will tend to select fertility in the spring brood and longevity in the autumn, but with a time-lag of one generation between selection and potential expression. The mechanism of selection in such a system must be very complicated.

In mammals some selective advantage would also presumably attach to longevity where older males are polygamous and younger males compete for the remaining females (deer, baboons). The solipsist model of selection operating on 'the individual' can obviously be upset by any selection pressures introduced into the system by interaction between individuals, and by community-patterns of ecological behaviour in the species; the idea of an 'individual' animal unsupported by the rest of the ecological community in which it lives is in fact unbiological, and large unpredictable selection pressures affecting the life-span may well arise from such hidden social relationships.

In spite of this criticism, the theory of senescence as a measure of declining selection-pressure is important. The declining evolutionary importance of the individual with age may be expressed in another way in the 'morphogenetic' senescence seen in mammals. At the point where a system of differential growth ceased to be regulated by forces which arose from natural selection, it would cease to be under effectively direc-

tional morphogenetic control, and would resemble an automatic control device which has run out of 'programme'. In any such system the equilibrium must be increasingly unstable. These two views of senescence, as accumulation of delayed lethal or sublethal genetic effects, and as a withdrawal of the evolutionary pressure towards homoeostasis with increasing age, are complementary, though probably only partial, pictures of its evolutionary significance. The concept of senescence as exhaustion of programme also restores a far greater unity to our definition of ageing, which includes a great many effects *having little in common beyond their destructive effect on* homoeostasis. All such effects fall within the idea of deterioration lying outside the 'terms of reference' of each species, as laid down by natural selection. The 'flying bomb' which failed to dive on its objective would ultimately 'die' either of fuel exhaustion, or through wear in its expendable engine. If its design had been produced by evolution, and its evolutionary relevance ceased at the moment of passing its objective, or decreased as a function of the distance flown, both these events would be outside the programme laid down by the selective equilibrium, as they were outside the calculation of the designing engineers. Death in such an expendable system may result from one of many factors, and even, as Bidder recognized, from the consequence of processes which contribute to fitness during earlier life, such as systems of differential growth. We shall find a good deal of gerontology *is* primarily the study of a living system's behaviour after its biological programme is exhausted. The various evolutionary explanations of ageing already combine to offer us some idea of the reasons why this may be so.

2

THE DISTRIBUTION OF SENESCENCE

2·1 *Character of the Evidence*

To find out which animals exhibit an increasing mortality with increasing age, we should ideally keep large numbers of each species, or of representative species, from birth to death, under optimal conditions of captivity. In point of fact, apart from the impracticability of keeping any significant number of species in this way, the results would be both artificial and potentially misleading. It is possible to invent about animal senescence a paradox rather analogous to the principle of physical uncertainty: it is 'virtually unknowable' or, in other words, meaningless to ask, whether certain organisms are 'susceptible to senescence', because the organism is biologically dependent on its environment: in the wild state these forms never normally live long enough to reach senescence, while domestication or protective interference with the environment brings about changes in physiology and behaviour which produce effectively a different organism. The object of the paradox is to point out the fruitlessness of argument over 'potential' behaviour which is practically unrealizable. Almost all our detailed knowledge of senescence comes either from the observation of man, or of domestication-artefacts such as the laboratory mouse or the laboratory strains of *Drosophila*. In the wild state it is most unlikely that any species of *Mus* or of *Drosophila* reaches old age with sufficient regularity to be subject to study. In most cases we are creating for study a state which has no part in the life cycle as it has been shaped by evolution, but is at most a potentiality. This must be taken into account on every occasion when theories of the evolution of senescence are being based on the appearance of senescence in domestic animals.

The Distribution of Senescence

In comparative studies of animal senescence we have three main types of information: single records of the extreme recorded longevity of different species under various conditions; observations on the composition of natural populations,[1] and marking experiments, which give a measure of longevity and mortality under natural conditions; and life-tables and comparable material plotted for animals under domestic and laboratory conditions, which indicate the susceptibility of these species to eventual senescence, either by measuring the force of mortality, or by measuring subsidiary age-characters such as reproductive capacity. Studies of *senescence in domestic animals* are singularly deficient, since apart from individual pets of various phyla neither farmers nor laboratories are usually interested in maintaining their stocks throughout the whole life-cycle and on into senescence. While there are extensive data on the early development of almost all animals of economic importance, the senile period is a virtually unworked biometric field. The literature does not even contain life-tables for representative species of each class of vertebrate. There is only one published life-table for birds in captivity (domestic fowls—Gardner and Hurst, 1933) and that is incomplete. No life-table appears to have been published for any reptile or fish, including common and short-lived aquarium species, or even for dogs or cats. Apart from man, adequate or partially adequate actuarial data exist in the literature for the following animals in captivity:

Mice (Kobozieff, 1931; Murray and Hoffman, 1941; Grüneberg, 1951, etc.) (Fig. 31).
Rats (Slonaker, 1912; Wiesner and Sheard, 1934).
Rattus natalensis (Oliff, 1953).
Voles (Leslie and Ranson, 1940) (Fig. 30).
Sheep (partial) (Kelley, 1939).
Fowls (Gardner and Hurst, 1933).
Limnaea (Gastropoda) (Winsor and Winsor, 1935; Baily, 1931) (Fig. 28).
Agriolimax (Gastropoda)(Pearl and Miner, 1935) (Fig. 5*c*).

[1] Methods of age determination in fish, molluscs and mammals have been well reviewed (*Trans. N.Y. Acad. Sci.*, **16**, no. 6, 1954) and their value criticized.

Drosophila (Diptera) (Pearl, 1928; Pearl and Parker, 1922, 1924; Gonzalez, 1923; Alpatov and Pearl, 1929; Alpatov, 1931; Pearl and Miner, 1935; Bilewicz, 1953).
Aëdes aegypti (Diptera) (Kershaw, Lavoipierre and Chalmers, 1953).
Acrobasis caryae (Lepidoptera) (Pearl and Miner, 1936).
Fumea crassiorella (Lepidoptera) (Mathes 1951) (Fig. 26).
Telea polyphemus (Lepidoptera) (Pearl and Miner, 1935).
Bombyx mori (Lepidoptera) (Alpatov and Gordeenko, 1932).
Tribolium confusum, *T. madens* (Coleoptera) (Park, 1945; Pearl, Park and Miner, 1941) (Fig. 36).
Cockroaches (*Blatta orientalis*, *Periplaneta americana*) (Rau, 1924; Griffiths and Tauber, 1942).
Bees (Ribbands, 1952, 1953).
Locusts (Bodenheimer, 1938).
Daphnia (Cladocera) (McArthur and Bailey, 1926; 1929a, 1929b; Ingle, Wood and Banta, 1937; Dunham, 1938; Anderson and Jenkins, 1942).
Latrodectes (Arachnida) (Deevey and Deevey, 1945) (Figs. 34, 35).
Rotifers (Jennings and Lynch, 1928; Lynch and Smith, 1931; Miller, 1931; Edmondson, 1945a, b; Lansing, 1942 etc.), Figs. 20, 22, 23).
Hydra (Pearl and Miner, 1935) (Fig. 5*c*).

There must be others which have been overlooked, especially in the entomological literature. Some unpublished survival curves, mostly from populations too small for actuarial treatment, are given in the text figures:

Lebistes reticulatus (teleost) (Fig. 18*a*).
Night heron (*Nycticorax nycticorax*). (Fig. 9).
African Ibis (*Threskiornis aethiopicus*) (Fig. 9).
Orkney vole (*Microtus orcadensis*) (Fig. 10).
Patagonian cavy (*Dolichotis patagona*) (Fig. 11).
Mouflon sheep (*Ovis musimon*) (Fig. 12).
Irish wolfhounds (Fig. 13).

Figs. 9–12 are prepared from data in the records of the London

Zoo, by kind permission of the Director, and Fig. 13 from data sent me by Miss D. Gardner.

Maximum longevity records of animals species have a definite, but limited, use in giving a comparative picture of the possible longevity in different forms. They can give no direct evidence of the distribution of senescence, but they can provide an important test of a number of general theories—those based, for example, on the exhaustion of neurones (Vogt and Vogt, 1946; Bab, 1948) are difficult to reconcile with the variation in specific age and potential longevity between closely-related forms. A large scatter of maximum recorded ages is in itself suggestive, but not of course demonstrative, evidence of an indeterminate life-span, except in cases where it is evidence only of improving cultural methods and better understanding of the requirements of the animal under laboratory or domestic conditions. For a very large range of species we can readily infer a 'potential' age which is never attained, either in the wild, because of accident and predation, or in captivity, because the animals cannot be kept alive in captivity—the 'potential' longevity of snakes, chamaeleons (Flower, 1925, 1937) or mammals of little known habits (pangolins—Flower, 1931) are cases in point. 'Concerning the length and brevity of life in [illegible]

[illegible]

off' (*Historia Vitae et Mortis*). With most birds, fully domestic mammals, hardy reptiles such as tortoises, and man, however, maximum records can be taken to represent in some real degree [illegible]

or at least not contradict them, to be available as working hypotheses.

2·2 *Maximum Longevities in Animals*

Apart from the observations collected by Bacon, which were remarkably critical and accurate compared with the wildness of later estimates, the accurate study of animal life-spans virtually

begins with the enormously painstaking studies of Chalmers Mitchell (1911) and Flower (1925, 1931, 1935, 1936, 1937, 1938 [1]) in purging a vast body of legendary and anecdotal material which encumbered the subject. Much of this legendary material unfortunately persists in other books and papers (*Tabulae Biologicae*—Heilbrunn, 1943; Nagornyi, 1948; Hammond and Marshall, 1952; Schmidt, 1952; Wurmbach, 1951) deriving their data from Korschelt (1922). The scepticism of Flower's papers was very valuable, in view of the exorbitant claims made for parrots, elephants and so on, but it seems probable that birds, in particular, are in fact capable of living considerably longer than Flower's maximum figures suggest. Better data may, in time, become available, though the value of such records is still not sufficiently widely appreciated and many opportunities must have been lost through failure to keep track of individual specimens. No recent writer has dealt equally painstakingly with the longevity of invertebrates.

The data on vertebrate senescence which follow are those of Flower, except where otherwise stated. Some more recent re- [illegible] 1939, 1940, 1942).

2·2·1 MAMMALS

The longest-lived species is man. *Elephas indicus* is known to reach 60 years: a few individuals may reach or exceed 70 in captivity (77?—Mohr, 1951). The only other mammals which are [illegible] ass (47 years?—Flower MS.). Many larger mammals, including baboons and other large primates, cats, bears, African elephant, equines, tapirs, can approach or exceed 30 years (Chimpanzee,

[1] Those references marked 'Flower MS.' refer to the card-index of data [illegible]

39, Tomilin, 1936; Baboon, *Papio papio*, 27—Duetz, 1938; *P. anubis* 30+—Krohn, in press; Gibbon, *Hylobates lar*, 32+—Duetz, 1938; domestic cat, 31—Mellen, 1939, 1940; 27, Comfort, 1955: Chapman's zebra, 40—Weber, 1942: *Echidna*, nearly 40 years—Duetz, 1942). A large group, including almost all ruminants, many medium-sized herbivores and carnivores, large bats and the larger rodents (beaver, capybara, the domestic rabbit) have recorded maximum ages between 12 and 20 years (Golden agouti, 15—Duetz, 1938). The maximum ages of very many rodents and small carnivores are not accurately established, since few specimens have been kept, but it is likely that a very large group among these forms has a potential life-span approaching ten years. The small Chiroptera certainly have a much longer life than most mammals of comparable size —ringed horseshoe bats have been recovered after at least 7 years (Bourlière, 1947). This agrees with their slow rate of reproduction.

The shortest-lived mammalian group (< 5 years) includes rats, mice, voles, and other small rodents, and the small insectivores. (Rat—4 years 8 months in a white rat probably already 1 year old—Donaldson, 1924; laboratory mouse, 3 years 3 months—Kobozieff, 1931; *Micromys minutus*, nearly 4 years—Pitt, 1945; golden hamster (*Cricetus auratus*), usually

)eansley, 1938;

;—Flower MS;

guinea pig, 7 years 7 months—Rogers, 1950; *Blarina*, 18 months —Pearson, 1945; *Sorex fumeus*, 13–14 months—Hamilton, 1940.) The real life-span of whales has never been established, but it is almost certainly not more than 30–50 years at the most, and probably less. The age of maturity of whales has been placed as low as 2 years (John, 1937). Ruud *et al.* (1950) found that blue whales reach sexual maturity in about 5 years—no individual in their very large sample was apparently older than 12 years,

T... life-span of dolphins in the

Detailed records of many other mammalian species are given by Flower.

Recent data on the longevity of seals were reviewed by Laws

(1953), upon the basis of tooth sections. Captive records include *Otaria byronia*, 23 years, *Eumetopias stelleri*, 19 (Flower, 1931); *Zalophus californianus*, 23; *Arctocephalus pusillus*, 20 (Bourlière, 1951); *Phoca vitulina*, 19 (Sivertsen, 1941); *Halichoerus grypus*, 41–2 (Matheson, 1950). In the wild, *Callorhinus ursinus* has reached 21 + years (Schaffer, 1950); *Mirounga leonina* ♂ 20; ♀ 18 (Laws, 1953).

The *maximum age records of horses and domestic pets* are of importance because these animals are the only mammals kept throughout life in sufficient numbers to give any estimate of the extreme age for the species. In spite of the likelihood of exaggeration and mistake, records of domestic pets kept singly, throughout life, by intelligent witnesses, provide evidence as good as that from laboratory stocks and sometimes better than that from zoos, since reliable mnemonic evidence is better than unreliable documents.

The known range of maximum ages for some domestic species is given below. The figures in brackets represent unauthenticated claims within the range of possibility, based as a rule on evidence which can be neither assessed nor dismissed.

Horses certainly exceed 40, may perhaps exceed 50 years—most higher claims refer to ponies. Smyth (1937) reported a 46-year-old brood mare which foaled for the 34th time at 42—this case appears authentic. (Horse, 62—Flower, 1931; jennet, reputed 60—Wright, 1936; pony, 54—Rothschild *fide* Flower, 1931; Shetland pony, 58—*The Times*, 3/5/44; roan pony, 52—*The Times*, 12/4/44; Iceland pony, 47—*The Times*, 7/8/34; *many records between* 40 and 45.) A zebra has reached 40 in captivity (Weber, 1942). *Asses*—probably exceed 40 (47—Flower MS. from a press report; but an 86-year-old ass in *The Times*, 29/11/37, can hardly be taken seriously). A 48-year-old mule is reported (Galea, 1936).

Domestic goats, 15 and probably up to 20 years (20 years 9 months—female wild goat, London Zoo).

Carnivora: *cats* are the longest lived of the small domestic mammals. Mellen (1940) from questionnaires sent out in Canada and the U.S.A. obtained these records: gelt males, 21, 21, 22, 23, 24, 24, 25, 28, 31 years; entire males, 23, 24, 26; females, 21, 21, 22, 31. These were owners' estimates, but at

least one 31-year record was well supported. 33 years has been claimed (Mellen, 1910). Figures for cats in England in recent years included at least ten apparently authentic cases over 20, and one gelt male alive at 28 (Comfort, 1955).

Dogs very seldom exceed 18 years, and only exceptionally reach twenty. In many breeds the limit is far lower. There are remarkably few claims of greater longevity in the literature (34 years, Lankester, 1870).

Rodents: the *rabbit* can almost certainly exceed 15 years. (10 years 3 months in the laboratory—Tegge 1936; buck 13 years—Barrett-Hamilton 1911; buck, chinchilla × Belgian hare, 11 years two cases; English buck 14 years, both authenticated —Comfort 1955.) Flower MS. contains a plausible correspondence with the owner of a rabbit (doe) which was said to have exceeded 18 years and was still alive.

2·2 2 BIRDS

Flower's longest 'incontestable' record in captivity (Flower, 1925, 1938) was 68 years in *Bubo bubo*. This is probably too low. Records exceeding 70 years in parrots, swans, and several large predators given by Gurney (1899), though less fully proven, are probably substantially correct.

The maximum life-span in birds is not proportional to size. It is materially longer than in mammals of comparable size and activity. Many species can live 30–40 years, including small and active birds such as pigeons (Flower 1938, Fitzinger 1853: *Streptopelia risoria* 40 years, *Columba livia* 30 years, *Goura cristata* ♂ 49, ♀ 53 years), while even the smaller passerines have a potential life of 10–15 or more years in captivity (29 years in a chaffinch—Moltoni, 1947) and ages of this order are occasionally reached even in the wild state (Perry, R. 1953). It has been properly remarked that

A robin redbreast in a cage
Lives to a tremendous age.

Extensive aviary records are given by Chalmers Mitchell (1911).

TABLE I

MAXIMUM RECORDED LONGEVITIES IN 45 SPECIES OF BIRD
(Flower, 1938)

	Years Proven	Years Reported
Eagle owl (Bubo bubo)	68	
Greater sulphur-crested Cockatoo (Cacatua galerita)	56	69, 80, 120
Bateleur Eagle (Terathopsius ecaudatus)	55	
Vasa Parrot (Coracopsis vasa)	54	
Condor (Vultur gryphus)	52	
White Pelican (*Pelicanus onocrotalus*)	51	
Grey Parrot (Psittacus erythacus)	49	73
Golden-naped Parrot (Amazona auropalliata)	49	
Australian Crane (Megalornis rubicunda)	47	
Golden Eagle (Aquila chrysaetos)	46	80
Adalbert's Eagle (Aquila adalberti)	44	
Blue-and-yellow Macaw (Ara ararauna)	43	
Grey Crane (Megalornis grus)	43	
Leadbeater's Cockatoo (Cacatua leadbeateri)	42	60
Caracara (Polyborus tharus)	42	
Chilean Eagle (Geranoaëtus melanoleucus)	42	
White-tailed Eagle (Haliaetus albicillus)	42	
Sarus Crane (Megalornis antigone)	42	
Rough-billed Pelican (Pelicanus erythrorhynchos)	41	
Manchurian Crane (Megalornis japonensis)	41	
Asiatic White Crane (M. leucogeranus)	41	
Herring gull (Larus argentatus)	41	44, 49
Banksian Cockatoo (Calyptorrhynchus banksii)	40	
Bare-eyed Cockatoo (Cacatua gymnopis)	40	
Western slender-billed Cockatoo (Licmetis pastinator)	40	
Tawny Eagle (Aquila rapax)	40	
King Vulture (Sarcorhamphus papa)	40	
Ceylon Fish Owl (Ketupa zeylonensis)	39	
Cinereous Vulture (Aegypius monachus)	39	
Red-and-blue Macaw (Ara macao)	38	64
Griffon Vulture (Gyps fulvus)	38	117
American Crane (Megalornis americana)	38	
Californian Condor (Pseudogryphus californianus)	37	
Shoebill (Balaeniceps rex)	36	
Domestic goose (Anser anser domesticus)	35	80
Slender-billed Cockatoo (Licmetis tenuirostris)	34	85
Canadian Goose (Branta canadensis)	33	47
Orange-winged Parrot (Amazona amazonica)	30	71
Roseate Cockatoo (Cacatua roseicapilla)	30	47
Domestic Pigeon (Columba livia domestica)	30	35
Domestic Dove (Streptopelia risoria)	30	42
Emu (Dromiceius novae-hollandiae)	*28*	*40*
Ostrich (Struthio camelus)	27	40
Egyptian Vulture (Neophron percnopterus)	23	101
Crowned Pigeon (Goura cristata)	16	49, 53

2·3 REPTILES

The longevity of tortoises is one of the few popular beliefs about animal life-span which is correct, though it has been exaggerated. There is no clear evidence that the larger species

TABLE II

MAXIMUM RECORDED LONGEVITIES OF CHELONIANS
(Data from Flower, 1937, except where otherwise stated)

		Years
Testudo sumeiri	Marion's Tortoise	152 +
elephantopus	Galapagos Tortoise	100 +
graeca	Greek Tortoise	102, 105
daudini	Daudin's Tortoise	100 +
hermanni	Hermann's Tortoise	90 +
radiata	Radiated Tortoise	85 +
gigantea	Giant Tortoise	68-180
sulcata	Spurred Tortoise	42
marginata	Margined Tortoise	20
Terrapene carolina	Carolina Box-tortoise	123 +
		118 + Dittmars, 1934
		129* Oliver 1953
		80 + * Deck, 1927
		65* Edney and Allen, 1951
Emys orbicularis	European Pond-tortoise	70–120 Rollinat, 1934
Macroclemmys temminckii	Snapping Turtle	58 + , 47 Conant and Hudson, 1949
Clemmys guttata	Speckled Terrapin	42 +
Pelusios derbianus	Derby's Terrapin	41 +
subniger		29 + Conant and Hudson, 1949
Sternotherus odoratus	Stinkpot Terrapin	53 + Conant and Hudson, 1949
Kinosternon subrubrum	Pennsylvania Terrapin	38 +
Chelodina longicollis	Longnecked Terrapin	37 +
		31 + Conant and Hudson, 1949
Caretta caretta	Loggerhead Turtle	33
Malaclemmys centrata	Diamond-backed Terrapin	?40 Hildebrand, 1933
Cuora trifasciata	Three-banded Terrapin	26 +
Geoclemmys reevesi		24 + Conant and Hudson, 1949

* Marked individual recovered in the wild.

are potentially very much longer-lived than some small forms. The maximum authenticated records include *Testudo sumeirii*, 152+ (years); *T. elephantopus* 100+; *T. graeca*, 102, 105; *T. daudini*, 100+; *T. hermanni*, 90+; *Emys orbicularis*, 70–120 (Flower, 1925, 1937; Rollinat, 1934; Korschelt, 1931); *Terrapene carolina*, 118+ (Ditmars, 1934), 88+ (Deck, 1926), 64 (Edney and Allen, 1951), the last two in the wild. The age of the royal tortoise of Tonga, said to have belonged to Capt. Cook, and still living, is unsupported by documents, but may well be authentic.

The longevity of turtles and luths (Parker, 1926, 1929) and of crocodiles has been assumed, upon a basis of recorded sizes, to be very great, though the longest captive record of a crocodile is 56+ years (Flower, 1937). *Alligator sinensis* has been kept 52 years (Lederer, 1941), and *A. mississippiensis* 41 years in the London Zoo (1912–53). The records of snakes are limited by their poor survival in zoos. (*Eunectes murinus*, 29 years (Flower, 1937), 28 (Perkins, 1948); *Epicrates cenchris* 27 (Perkins, 1948).) Lizards: *Anguis fragilis*, 33 years (Hvass, 1938), 32 (Flower, 1937), 27 (Thummel, 1938); *Sphenodon punctatus*, 28+ (Flower, 1937); *Heloderma suspectum*, 20 (Conant and Hudson, 1949); *Ophisaurus apodus*, 11 years 7 months (Conant and Hudson, 1949), 24 years (Perkins, 1948). The maximum life-span appears to be relatively brief in chamaeleons, but this may simply be due to failure to thrive in captivity.

2·2·4 AMPHIBIANS

Here again the figures in relation to size and growth give no very clear evidence that the life-span is sharply determined. The maximum records are in *Megalobatrachus* (52+ years—Flower, 1936; 65+ years—Schneider, 1932) but many small species are capable of very long life (*Triton* spp., 35 years—Smith, 1951; *Triturus pyrrhogaster*, 25—Walterstorff, 1928; *Amphiuma punctatum*, 25—Koch, 1952; *Triton marmoratus*, 24, 21—Wendt, 1934; *Pleurodeles waltl*, 20—Noble, 1931). *Siren*, 25 years, *Amphiuma*, 26—Noble, 1931; *Salamandra salamandra*, 24, *Bufo bufo*, 36, *Hyla coerulea*, 16, *Rana catesbiana*, 15, *Xenopus laevis*, 15 (Flower 1925; 1936), *Rana temporaria* 12+ years (Wilson 1950),

R. esculenta 14+, 16+, *R. temporaria* 9+ (Sebesta 1935), *Leptodactylus pentadactylus* 15 years 9 months (Conant and Hudson, 1949).

2·25 FISH

Seriously acceptable records of longevity in the larger fish are very few. The longest accepted by Flower are *Silurus glanis*, 60+ years, *Anguilla anguilla*, 55, *A. chrisypa*, 50 (Flower 1935). Some of the more celebrated legends of fish longevity (up to 170, 200, 300, or 400 years in carp, and 250 years in pike) are revived by Backmann (1938) and by Wurmbach (1951). 'Wenn auch diese Angaben hier und da übertreiben sein sollten', remarks Wurmbach, 'so kann doch gar kein Zweifel daran herrschen, dass der Karpfen wirklich ausserordentlich alt wird, und das Alter des Menschen weitaus übertrifft'—this is quite possibly true. Many exaggerated estimates have been based upon size, as extrapolations of the normal mean growth rate for the species—upon this basis, a 720 kg. sturgeon should be about 200 years old, and occasional examples weighing 1200 to 1600 kg. would be of fantastic antiquity. In no case, however, are any of these estimates supported by otolith or comparable studies, and the extrapolation is almost certainly unjustified. It is a matter of considerable biological importance to get proper age determination upon exceptionally large specimens of this kind.

The life-span of small fish is certainly limited in captivity (*Aphya pellucida*, 1 year; *Lebistes*, 1–2; *Xiphophorus*, 2–3; *Molliensia latipinna*, 3–4; *Betta pugnax*, 1½–2—Wurmbach, 1951). A few species of *Gobius* and *Latrunculus* must be regarded as annuals, even in captivity (Bourlière, 1946, Meyers 1952). In this field there is little new information since the seventeenth century. 'The life of fishes is more doubtful than that of land beasts, since, living below the waters, they are less observed. Dolphins are said to live about thirty years; this is obtained by experiment upon some of them, the tail being marked by cutting; they grow for ten years. In Caesar's fishponds were certain *Muraenae* found to have lived to the sixtieth year. Indeed, they were grown with long use so familiar, that Crassus the orator mourned for the death of one. The pike, of freshwater fish, is

found to live the longest, sometimes to the fortieth year. But the carp, bream, tench, eel and the like are not held to live above ten years. Salmon grow quickly and live not long, as do also trout; but the perch grows slowly and lives longer. How long the breath governs the vast bulk of whales and orcae, we have no certain knowledge; neither for seals, nor for innumerable other fish' [1] (*Hist. Vitae et Mortis*). Most of these figures are reasonably congruent with Flower's list.

2·2 6 INVERTEBRATES

Previous lists of invertebrate longevities (*Tabulae Biologicae*; Heilbrunn, 1943; Nagornyi, 1948, etc.), apart from the excellent data collected by Weismann (1891), almost all spring directly from the opinions of Korschelt (1922). These are based on data from the older literature, largely unsupported by exact references, some accurate, but others highly speculative. The type of evidence which has got into such lists is well exemplified by the 15–20 year life-span of the crayfish. This, though probably correct, appears to owe its origin to an aside by T. H. Huxley (1880) to the effect that 'it seems probable that the life of these animals may be prolonged to as much as fifteen or twenty years' (*The Crayfish*, p. 32). The large *Tridacna* may in fact be the longest-lived invertebrate, in view of high records of age in much smaller pelecypods, but the literature contains no information of any description about its life-span, and the relationship between great size and great age is perpetually being disproved in other animals. Of a supposedly 18-year-old *Helix pomatia* Korschelt writes elsewhere: 'Gewiss hat diese Angabe von vornherein wenig Wahrscheinlichkeit für sich, aber als

[1] 'Piscium vita magis incerta est, quam terrestrium, quum sub aquis degentes minus observantur. . . . Delphini traduntur vivere annos circa triginta; capta experimento in aliquibus a cauda precisa; grandescunt autem ad annos decem. Deprehensae sunt aliquando in piscinis Caesarianis muraenae vixisse ad annum sexagesimum. Certe redditae sunt longo usu tam familiares, ut Crassus orator unam ex illis defleverit. Lucius, ex piscibus aquae dulcis, longissime vivere reperitur; ad annum quandoque quadragesimum . . . at carpio, abramis, tinca, anguilla et huiusmodi non putantur vivere ultra annos decem. Salmones cito grandescunt, brevi vivunt, quod etiam faciunt trutae; at perca tarde crescit, et vivit diutius. Vasta illa moles balaenarum et orcarum, quamdiu spiritu regatur, nil certi habemus; neque etiam de phocis. . . . et aliis piscibus innumeris.'

unmöglich wird man dieser Langlebigkeit nach dem, was man von anderen Tieren weiss, nicht bezeichnen dürfen' [1] (1922, p. 36, footnote).

A proper survey of the longevity of invertebrates can hardly yet be undertaken—the information is mostly lacking. It seemed wisest in compiling Table III, which includes a few of the longest and most interesting invertebrate records, to give not only the record and source, but the type of evidence upon which the record is based. In invertebrates which metamorphose, length of larval life often depends entirely upon environment and food, while in other forms adult life can be punctuated by very long spells of diapause. Figures for these forms should therefore when possible indicate the circumstances of life. Larval life-spans have in general been omitted from Table III. The most reliable records are in all cases those of animals kept, like Labitte's (1916) beetles or the Edinburgh sea anemones (Ashworth and Annandale, 1904) under close observation in captivity. Evidence from growth rings requires very careful scrutiny. Some purely inferential evidence, as of the age of termite primaries, is probably reliable. There are also some surprisingly high records in the wild, especially for pelecypods, where the method of ageing by rings of growth has been well upheld by other evidence. The life-span of common invertebrates certainly remains a wide-open field for those with facilities and an unlimited capacity for taking pains, and one where any reliably-attested information is worth putting on record.

[1] 'No doubt these findings have little probability in themselves, but one cannot dismiss such longevity records as impossible, in view of what is known of other animals.'

TABLE III

MAXIMUM RECORDED LONGEVITIES OF VARIOUS INVERTEBRATE SPECIES BY PHYLA

(Ages in years unless specified)

c = information based on specimens in culture or captivity
w = information based on specimens in the wild
g = age estimated by examination of growth rings
h = case history (in parasitic forms)

Porifera			
Suberites carnosus	15	c	Arndt, 1941
Adocia alba	9	c	Arndt, 1941
Coelenterata			
Actinia mesembryanthemum	65–70		Dalyell, 1848
		c	Korschelt, 1922
Cereus pedunculatus	85–90	c	Ashworth and Annandale, 1904
			Stephenson, 1935
			Warwick, 1954 (personal commn.)
Platyhelminths			
Schistosoma haematobium	25	h	Kirkland, 1928
	28	h	Christopherson, 1924
Clonorchis sinensis	25	h	Moore, 1924
Gastrodiscus aegyptiacus	9	h	Christopherson, 1924
Taeniorrhynchus saginatus	>35	h	Penfold, Penfold and Phillips, 1936
Diphyllobothrium latum	29	h	Riley, 1919
'Echinococcus cysts'	56	h	Lawson, 1939*
Dugesia tigrina (= Planaria maculata)	6–7	c	Goldsmith, 1942
Dendrocoelum lacteum	5	?	Bresslau, 1928–33
Nematoda			
Loa loa	15	h	Coutelen, 1935
Wuchereria bancrofti	17	h	Knabe, 1932
Necator americanus	12	h	Sandground, 1936
Rotifera—see Table IV			
Annelida			
Eisenia foetida	3–4½	c	Rabes, 1901
Lumbricus terrestris	5–6	c	Korschelt, 1914
Allolobophora longa	5–10	c	
Sabella pavonina	>10	c	Wilson D. P., 1949
Arthropoda			
(Arachnida)			
'Tarantula' (aviculariid)♀	11–20	c	Baerg, 1915
Avicularia avicularia ♀	>7	c	Didlake, 1937
Tegenaria derhami ♀	7	c	*Savory, 1927*
Filistata insidiatrix ♀	10, 11	c	Bonnet, 1935

* See also Coutelen *et al.*, 1950, Davaine, 1877, Wardle and McLeod, 1952, pp. 116–17.

Arthropoda			
Physocyclus simoni	4	c	Bonnet, 1935
Teutana grossa ♀	6	c	Bacelar and Frade, 1933
Psalmopoeus cambridgii	5½	c	London Zoo, Flower MS.
Lasiodera curtior	4½	c	London Zoo, Flower MS.
(Crustacea)			
Astacus	15–25		inference Friedel, 1880
Homarus	50		inference Herrick, 1898, 1911
Leander serratus ♀	5–6		inference Solland, 1916
Oniscus asellus	4½	c	
Philoscia muscorum	4	c	
Porcellio scaber	3½	c	Collinge, 1944
dilatatus	3½	c	
Platyarthrus hoffmanseggi	5+	c	
Armadillium vulgare	4+	c	
Balanus balanoides	>5	w	Moore, 1934
(Insecta)			
Thysanura			
Ctenolepisma longicaudata	total 7	w	Lindsay, 1940
Ephemeroptera			
Cloëon dipterum	imago 4 wks	c	Vane, 1946
Isoptera			
Neotermes castaneus ♀ ♂	imago >25 yrs	w	Snyder, *fide* Howard, 1939
Nasutitermes–physogastric ♀	20–40	w	v. Hagen, 1938
'Termite primaries'	60–?	w	Richards, 1953
Lepidoptera			
Nymphalis antiopa	imago 12 wks	c	
Callophrys rubi	imago 6 wks	c	Frohawk, 1935
Maniola jurtina	imago 44 days	c	
Coleoptera*			
Blaps gigas	imago>10 yrs	c	
Timarcha sp.	imago> 5	c	Labitte, 1916
Carabus auratus	imago 3–1	c	
Dytiscus marginalis	imago< 3	c	Blunck, 1924
Prionotheca coronata	imago 6, 7+	c	London Zoo, Flower MS.
Akis bacarozzo	imago> 4	c	
Cybister laterimarginalis	imago 5½	c	Sharp, 1883
Hymenoptera			
Apis mellifica ♀	imago >5	c	Pflugfelder, 1948
Lasius niger ♀	imago >19	c	Goetsch, 1940
Stenamma westwoodi ♀	imago 16–18	c	Donisthorpe, 1936
Formica fusca ♀	imago 10+	c	Janet, 1904
♀	imago 15+	c	Lubbock *fide* Weismann, 1882
sanguinea ♀	imago 5+	c	Lubbock *fide* Weismann, 1882
Lasius niger ☿	imago >7	c	Lubbock *fide* Weismann, 1882
Formica fusca ☿	imago >7		

*For a discussion of the longevity of beetle larvae, see Howard 1939; also Latter 1935 (*Cossus*) Linsley 1938 (*Stromatium*).

Echinodermata			
Echinus esculentus	>8	w	Moore, 1935
Psammechinus miliaris	>6	c	Bull, 1938
Asterias rubens (*reaches sexual maturity*)	5–6	c	Bull, 1934
Marthasterias glacialis	>7	c	Wilson, 1954 (personal comm.)
Ophiothrix fragilis	>5	c	*Zool. Gart.*, 1930
Mollusca			
Patella vulgata	15	w g	Fischer-Piette, 1939
Acmaea dorsuosa	15	w g	Abe, 1932
Gibbula umbilicalis	5	w	Pelseneer, 1934
Trochus niloticus	12	w g	Rao, 1937
Viviparus contectus	4½ ♂	c	Oldham, 1931
	5 ♀	c	
viviparus	9	c	Geyer, 1909
Hydrobia ulvae	>5	c	Quick, 1924
Pila sp.	5	c	Flower, 1922
Haminea hydatis	4	w	Berrill, 1931
Planorbis corneus	6	c	Oldham, 1930
Limnaea luteola	3	w	Seshaiya, 1927
Physa gyrina	12–13 months	w	DeWitt, 1954
	14–15 months	c	
Abida secale	<3	c	*fide* Flower MS.
Helix pomatia	6–7	c	Kunkel, 1916
aspersa	5–6	c	Welch, 1901
(Cepaea) nemoralis	7	c	Brockmeier, 1896
hortensis	9	c	Lang, 1896
nem × hort hybrid	10	c	Cuenot, 1911
(Arianta) arbustorum	5	c	Kunkel, 1916
'Helix spiriplana'	15	c	Vignal, 1923
Eulota fruticum	5–6½	w c	Künkel, 1928
Hyalinia villae	5½	c	van der Horst, 1929
Limax cinereoniger	5	c	Oldham, 1942a, b
Geomalacus maculosus	6½	c	
Achatina zebra	6½	c	Longstaff, 1921
Rumina decollata	12	c	Vignal, 1919
Oxystyla capax (aestivating)	23	c	Baker, 1934
Ostrea edulis	>12	w g	Orton and Amirthalingam, 1930
Pecten jessoensis	>8	w g	Bazykalova, 1934
Megalonaias gigantea	54, 36	w g	Chamberlain, 1933
Quadrula sp.	>30	w, marked	Isely, 1931
	20–50	w g	Lefevre and Curtis, 1912
Margaritana margaritifera	>60	inference	Geyer, 1909 (see also Israel, 1913, Cuenot, 1911)
Cardium corbis	>16	w g	Weymouth and Thompson, 1930
Tivela stultorum	20	w g	Weymouth, 1923
Venus mercenaria	>40	w g	Hopkins, 1930
Siliqua patula	14–16	w g	Weymouth, 1931
Mya arenaria	>8	w g	Newcombe, 1935, 1936

TABLE IV

MAXIMUM RECORDED LONGEVITIES OF ROTIFERS

(Bibliography from Hyman, 1951)

Asplanchna sieboldii	2–3 weeks	c	Tannreuther, 1919
Proales decipiens	12 days	c	Liebers, 1937
sordida	22 days	c	Jennings and Lynch, 1928; Lynch and Smith, 1931
Cupelopagis vorax	40 days	c	Cori, 1925
Euchlanis triquetra	21 days	c	Lehmensick, 1926
Epiphanes senta	8 days	c	Ferris, 1932
Brachionus pala	12–19 days	c	Chu, 1934
Euchlanis dilatata	23 days	c	Liebers, 1937
Keratella aculeata	29 days	c	Kolisko, 1938
Epiphanes brachionus	17 days	c	Kolisko, 1938
Floscularia conifera	18 days	c	Edmondson, 1945
Lecane inermis	14 days	c	Miller, 1931
Philodina roseola	10 days	c	Spemann, 1924
citrina	21 days	c	Spemann, 1924
megalotrocha	17 days	c	Spemann, 1924
Rotaria macrura	58 days	c	Spemann, 1924
rotatoria	20–50 days	c	Spemann, 1924
Callidina sp.	5 months	c	Zelinka, 1891
Adineta vaga	15–22 days	c	Dobers, 1915
barbata	21 days	c	Dobers, 1915
Habrotrocha constricta	34 days	c	Dobers, 1915
Macrotrachela quadricornifera	2 months	c	Dobers, 1915
Mniobia russeola	30 days	c	Dobers, 1915

2·3 *Maximum Life-span in Man*

Human longevity records are even more notorious than those of animals. They depend largely on unsupported memory and tradition in a field where the emotional premiums of exaggeration are high. 'Furthermore, even though this satisfaction and vanity, of which we have spoken, were absent, yet such is the peculiar and perpetual wandering of the human Intellect, that it is more moved and roused by affirmatives than by negatives, whereas properly it ought to be just to both, nay even, in the forming of any axiom, the force of the negative instance is the greater.' (*Novum Organum*). King (1911) found in the 1911 census a discrepancy between the size of the 85–90 year-old age group and that of the next higher group, which was almost certainly due to exaggeration. William Thoms (1873), founder

of *Notes and Queries*, and Young (1899) devoted much time to exposing the pretensions of past supercentenarians. In some of the 'documented' cases, the life-span of father, son, and grandson of the same names were apparently conjoined in one record. Young's greatest authenticated record was a few weeks short of 111 years.

The actuarial probability of an individual's exceeding the age of 150 years, on the life-data of 1939, has been estimated at $(\frac{1}{2})^{50}$ (Greenwood and Irwin, 1939). Pütter (1921) calculated on a basis of German vital statistics for the years 1871–91 that ages over 105 were effectively impossible, and that for every million persons reaching 20 years, the number reaching 109 would be $4{\cdot}8 \times 10^{-10}$: 'danach wäre es nunmehr wohl an der Zeit, die Berichte über 120, 130, 140, 150 usw.-jährige dahin zu verweisen, wohin sie gehören: ins Reich der Fabel'. This scepticism has proved excessive, especially as regards the population-frequency of centenarians (see Freudenberg, 1949). The existence of supercentenarians cannot be disproved by statistical means unless the distribution of ages is really continuous, since ordinary life-tables have no defence against, say, a rare genotype with double the normal potential life-span. The number of persons reaching 100 years is in any event too small for statistically significant estimates of the rate of increase in the force of mortality after about 90 years of age. Pütter's estimate was based on the assumption that this increase continued at the same rate as in earlier life. The relation between observation and calculation in this part of the life-table is fully discussed by Greenwood and Irwin (1939).

Subsequent writers have been content to rely on direct observation, provided that only records supported by proper documentary evidence are taken seriously (Forster, 1945; Tomilin, 1938). The minimum requirements are these laid down by Thoms (1873)—documentary evidence of *birth* (or baptism), of *death or present age*, and of *identity*. The third of these, as Pearl (1928) points out, is commonly the key to false records of extreme age. The best of such evidence, from compulsory birth certification, has been available in England since 1837, and would now be available for records up to 118 years (1955). By critical standards of comparable severity the greatest

human age to be authenticated with reasonable certainty has been said to be 120 years (Fisher, 1923). A considerable number of cases between 110 and 115 years have also stood up to examination (e.g. Bowerman, 1939; Backman, 1945; Korenchevsky, 1947). The greatest age to be authenticated in England and Wales by actual birth certificate, however, is 109 years, while in one case the absence of a birth certificate indicated an age in excess of 111 years.

Claims of extreme longevity in particular districts abound. Metchnikoff investigated statements of this kind in Bulgaria and the Caucasus. Bazilievitch (1938a, b) led an expedition to investigate the celebrated longevity of Abkhasians, and examined several claimants in detail. Two of these were reputed to be over 130 years old. The evidence (identity papers and memory of events in the Caucasus during the early nineteenth century) is given by Bazilievitch in careful detail; much of it is extremely entertaining, but far from conclusive, although the subjects were certainly very old men (Bazilievitch, 1938b).[1] In recent years very large numbers of claims to extreme longevity have been made in Russia (e.g. Rokhlina, 1951; Nagornyi, 1948; Lukyanov, 1952; Nikitin, 1954). Dealing with the figures in the 1926 census of the U.S.S.R., which showed proportions of 3·5 and 3·8 centenarians *per thousand* gross population in Daghestan and Abkhasia respectively, as to 1·8 per million among Volga Germans, Tomilin (1938) says 'We must doubt the factual truth of these figures, since no documentary evidence of the age of persons who had passed the century mark was produced.' The analysed distribution of age-groups in the Abkhasian census shows exactly the same deficiency in the 85–89 and 95–99 year groups, compared with the 90–94 and 100+ groups, which was observed by King (1911) in England. 'Without special documentary evidence of the accuracy of these age-data, we cannot conclude definitely that the relative number of persons reaching the age of 100 and over in the general

TABLE V

NUMBER AND MAXIMUM AGES OF CENTENARIANS DYING IN ENGLAND AND WALES

(Registrar-General's statistics)

Year	*Number and probable maximum age*	
	Men	*Women*
1940	20 (105)	102 (108)
1941	18 (112)	91 (108)
1942	12 (107)	79 (108)
1943	21 (108)	92 (106)*
1044	21 (109)	85 (105)*
1015	19 (105)*	71 (106)*
1946	22 (105)*	94 (108)*
1947	19 (106)*	97 (108)*
1948	19 (103)*	107 (115)
1949	27 (104)*	133 (106)*
1950	22 (102)*	131 (107)*
1951	33 (104)*	142 (109)*
1952	24 (105)*	147 (107)*

* = verifiable by birth certificate.

mass of the population of Abkhasia is really higher than in the population of Russia' (Tomilin 1938). In America, Nascher's investigation of John Shell, reputed to be 131, showed him to be in fact about 100 years old (Nascher 1920). In England and [illegible] may have reached 115 years, and had certainly reached 111.

Sporadic records of supercentenarians such as Old Parr, whose tomb in Westminster Abbey credits him with an age of 152 years, whose body was examined by Harvey, and whose complete lack of documentation was exposed by Thoms (1873), occur in almost all cultures: a long series of similar anecdotes is given by Gould and Pyle (1898). The best recent summary of these often-paraded examples is that of R. T. Gould (1945). Though in most cases the stories conform closely to the childhood fantasy of 'going on living for almost always', they may also indicate that authenticated records do not yet represent the extreme of human longevity under all conditions. There is some ground, apart from the absence of critical record in backward countries, to associate extreme *individual* longevity

with a low rather than a very high standard of living throughout life (Gumbel, 1938), an argument which fortunately has not so far been advanced to justify starvation as a social policy. Extreme records in man, occurring in excess of statistical probability, are chiefly of interest in suggesting that after a certain age the rate of increase in the force of mortality is not maintained, either by reason of selection or from other causes.

2·4 *Distribution of Senescence in Vertebrates*

Actuarial senescence is known, or reasonably assumed, to occur in all mammals, provided they live long enough. It is less easily recognized, but apparently equally universal, in birds. There are apparently no satisfactory life-table studies of birds under domestic conditions apart from a single paper on fowls (Gardner and Hurst, 1933), but individuals kept as pets certainly become increasingly enfeebled after an age which is fairly constant for the species, and the reproductive senescence of poultry, marked by a steep decline in egg production, is well-known to farmers (Clark, 1940; Brody, 1945; Fig. 14). This

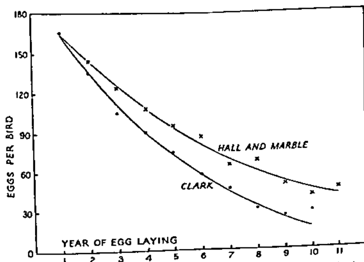


FIG. 14.—The decline in egg production in successive years of laying (drawn from the data of Clark and of Hall and Marble).

decline can be reduced by mild hypothyroidism (Turner and Kempster, 1948) The pair of crowned pigeons which lived, according to Fitzinger (1853) for over 40 years, mated and laid throughout life, but hatched no offspring after the age of 18 or 20 years (Flower, 1938). Spermatogenesis likewise appears to decline (Payne, 1952). The life-span of birds is longer in proportion to size and metabolic rate than that of mammals, and the scatter of age in senescence as shown by aviary records appears, superficially at least, to be rather greater within a species.

We are familiar with the ageing of warm-blooded animals because we keep them. It is among the 'cold-blooded' vertebrates that the real uncertainty begins. We keep fish, but only the smaller forms—we do not, apart from zoological gardens and occasional pet tortoises, keep reptiles; as for amphibia, Hilaire Belloc wrote uncontrovertibly concerning lonely people who keep frogs that

by the way
They are extremely rare.

The general assumption that all vertebrates must necessarily undergo a senescence at least superficially similar to that of mammals has prejudiced even those biologists who have kept frogs for long periods, with the result that very little real information unbiassed by this assumption has been published. Very possibly the assumption may prove to be correct, but it cannot be lightly made. It is evident that some senile change, in the form of an accumulation of injuries, must occur in all vertebrates with the passage of time, and be reflected in the force of mortality. But this effect is certainly small and inconstant compared with the 'morphogenetic' senescence which determines the life-span of mammals. It is this morphogenetic component which we are concerned to detect and estimate in lower vertebrates. Unfortunately for such a study, the life of many of these creatures, whether it ends in senescence or not, is, as we have seen, long enough to make ordinary short-term laboratory observation useless.

Bidder's opinions on the relation between perpetual youth and continuing growth have already been quoted (p. 12).

Three types of growth-pattern are theoretically possible in vertebrates—growth to a maximum size, ceasing when this is reached: growth *toward* a limiting size which is approached [illegible] theoretically do so in such a way that, given a sufficiently long life, *any* final size could be reached. These last two modes of growth correspond to convergent and divergent series. Thus in the series

$$(1)\ 1 + \tfrac{1}{2} + \tfrac{1}{4} + \tfrac{1}{8} \ldots \lim 2,$$

and the series

$$(2)\ 1 + \tfrac{1}{2} + \tfrac{1}{3} + \tfrac{1}{4} + \tfrac{1}{5} \ldots,$$

the increment at each term decreases (the specific growth rate falls), but whereas in (1) the series tends to a limiting size (specific size), in (2) it does not, and can be indefinitely continued so that any sum is ultimately attained. The terms 'indeterminate growth' and 'indeterminate size' have been differently used by different writers. D'Arcy Thompson wrote, 'It is the rule in fishes and other cold-blooded vertebrates that growth is asymptotic and size indeterminate' (1942). If the growth of an animal is in fact asymptotic, its size is limited by the sum of the asymptotic series. 'Indeterminate' growth without limit, but with a decline in the specific growth-rate, strictly follows the pattern of the divergent series. For this reason it would be desirable, but it is not empirically possible, given real biological material, to distinguish between 'asymptotic' and 'indeterminate' growth. In both cases the rate of growth declines with advancing age; but in the second case the potential size is unlimited.

Distinctions of this kind, however, are based upon the fitting of equations to points derived by averaging observations upon populations of animals, and in spite of the real value of such biometric applications, in the study of growth-curves they have tended to lose contact with the real behaviour of observable material. It is possible in practice to distinguish only between species, or particular populations of a given species, which

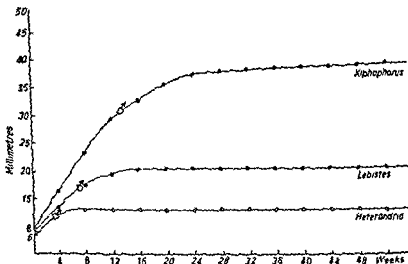


FIG. 15 (*a*).—Growth in length (mm.) of male fish of the genera *Xiphophorus*, *Lebistes* and *Heterandria* during the first year of life. Sexual maturity is indicated by ♂ (from Wellensieck, 1953).

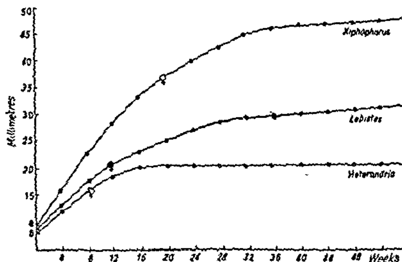


FIG. 15 (*b*).—Growth in length of female fish of the genera *Xiphophorus*, *Lebistes* and *Heterandria* during the first year of life. Sexual maturity is indicated by ♀ (Wellensieck, 1953).

continue throughout life to increase tangibly in size, given suitable conditions, and forms where the maximum size is reached relatively early in life, is fixed for the species, and does not increase further with increasing age even under the most favourable conditions. The chief obstacle to wide generalization about the determinacy or indeterminacy of growth in lower vertebrates, and in other forms such as pelecypods, lies in the fact that arrest of growth at an *apparent* specific size can be brought about by environmental conditions. In some cases growth can be resumed after such an arrest—in others, apparently, it cannot. Even less is known of the effect of these phenomena on the life-span than is known of the normal ageing of such forms. Differences are also substantial within each of the main groups of poikilothermic vertebrates. In many reptiles and small fish, continued growth after a relatively early age is no more evident than in the male rat. In amphibia, 'many species, particularly some tropical forms, seem to have an absolute size, which the males soon attain, but this does not hold for many salamanders, nor for some Northern frogs' (Noble, 1931). In many cases the male has an absolute size and the female has not. If enough data were available, the variety of growth-patterns is more than sufficient to test Bidder's hypothesis—unfortunately, corresponding data upon age/mortality relations are almost entirely lacking.

The idea of a 'self-maintaining' vertebrate is not impossible *ex hypothesi*. It is in fact what we should expect if growth-cessation is an equilibrium process, if there is no important process of differential growth at work, and if there is no qualitative change in the regenerative power of cells throughout adult life. It is not self-evident, though it might be true, that an animal should be obliged to increase in size in order to retain the power of carrying out running replacements. It seems reasonable for our purposes to regard an animal of 'indeterminate' growth as one in which the probability of nursing an individual to the point at which increase in somatic size has ceased is infinitely small, and an animal of 'indeterminate' life-span as one in which the survival rate under favourable conditions is substantially independent of age, however long a population of that animal is observed from birth.

In all the groups whose susceptibility to senescence is doubtful, there is wide variation in life-cycle and growth-pattern, which is very probably reflected in differences of their capacity for age changes. Some aquarium species of fish certainly 'age' as judged by their declining reproductive powers: in the larger sea fish this has not been clearly demonstrated. The contradictory views of fish senescence given to Flower (1935) by two acknowledged authorities, one on aquarium and the other on marine ichthyology, and based on small and large teleosts respectively, are possibly both correct. In other forms there is an obvious sex difference in growth-maintenance, in longevity, or in both. The specific age might also be indefinite in animals which nevertheless became more liable to die, as individuals, with increasing age. It was implied by Ricker (1945) that fish might senesce individually, i.e. undergo a waning of vitality and resistance with age, but that there is no sharp *specific* age—the life-span of each individual would be limited by senescence, but the senile process would reach its critical point at a much more variable age than in mammals: as if the menopause in human beings were to occur with approximately equal probability in any year after the menarche. Such senescence would be real, but could not readily be detected actuarially.

Very nearly all these problems require abundant new data to settle them finally. The general evidence of the distribution of vertebrate senescence which will be given here is both fragmentary and equivocal. It does, however, contain some facts which suggest that Bidder's hypothesis is too simple and that the *manner* of growth-cessation, rather than the fact of it, is the main determinant of the mammalian pattern of senescence.

2·4·1 FISH

The 'indeterminate' growth of fish, on which Bidder based his hypothesis, has often been discussed (Hecht, 1916; Keys, 1928; Huxley, 1932; Vaznetzov, 1934; Thompson, 1942; Wellensieck, 1953). Many large species of teleosts can continue to grow throughout life, and the rate of decline of their growth-rate is considerably slower than e.g. in most reptiles. The *locus classicus* of continued growth without evidence of senescence, actuarial or reproductive, is the female plaice. Here the evi-

dence supports Bidder in that growth in the male plaice ceases relatively early, and there is evidence that it has a shorter life-span than the female (Wimpenny, 1953). On the other hand, in many small teleosts reproductive senescence is known to occur, and both the sexes appear to exhibit specific age, in spite of the fact that growth in the female may continue throughout life. The reproductive failure of many teleosts with increasing age is familiar to aquarists. So is the tendency of particular species to have a limiting age, although there have previously been no published life-tables for any teleost in captivity by which this impression could be confirmed. The growth of some small teleosts has been studied (Felin, 1951; Wellensieck, 1953).

There is a good deal of evidence that small teleosts, and perhaps teleost species generally, undergo both reproductive and actuarial senescence comparable to that of mammals. The most dogmatic assertions on this score are those of pathological anatomists. On the basis of concretions occurring in the testis of a single teleost species (*Astyanax americanus*), Rasquin and Hafter (1951) hold that the 'appearance of senility changes shows that the teleosts conform to the common vertebrate pattern of ageing despite a widespread misconception to the contrary'. The decline of fertility in some aquarium species provides more solid evidence in support of this view. Many species of fish are in any case exposed to a specialized series of fluctuations in mortality associated with reproduction—the difficulties of treating these fluctuations as a form of senescence in those species which always die after breeding, such as the male of *Callionymus* (Chang, 1951) and the lamprey, are indicated by observations upon other fish in which there are a limited number of survivors from each breeding season, and these thereafter acquire a new lease of life. It is doubtful if any cyclical or potentially cyclical change in mortality can properly be called senile. In *Callionymus lyra* in the wild, the male appears to live 5 and the female up to 7 years. The males disappear, probably [illegible] water, after [illegible] hird, fourth, [illegible] growth, and probably breed more than once (Chang, 1951). In such a case,

the late-developing females would very probably have a longer total life-cycle.

Studies of wild populations are almost always conducted under conditions where the standing force of mortality throughout life is very high, and they therefore give little information about mortality trends in the latter part of the life-cycle of the longer-lived forms. Excluding the very high larval mortality, populations of many species of fish, studied in the wild, show an age structure and a pattern of death similar to that found in birds, i.e. a high constant mortality unrelated to age and a virtually constant expectation of life (Frost and Smyly, 1952 (Fig. 16); Deevey, 1947). Substantial differences in life-span may be dictated by availability of food organisms of a size suited to adult feeding, and by competition between the fry of the observed species and adults of other species. Some populations of minnows show apparent specific age which is exceeded in other populations of a closely-related species by a very large factor (Frost, 1943; Tack, 1940). In *Pimephales promelas*, Markus (1934) observed apparent specific size and specific age in all but a few exceptionally large individuals. This was apparently due to the fact that there was an overall mortality of 80 per cent following spawning; the survivors, and individuals which took no part in breeding during their first year of maturity, continued growth until the next breeding season. If reproduction is avoided, life may be prolonged—Bidder (1932) points out that eels, which, it is believed, normally die after spawning, live many years in captivity (Flower, 1925). Frost and Smyly (1952) found considerable differences in growth rates and in the form of the growth curve between brown trout inhabiting tarns and those inhabiting Windermere (Fig. 16). The age structure of the tarn population agreed well with a steady annual survival rate of 35 per cent between the second and eighth year of life. In these fish growth had become very slow, whereas in the Windermere population individual fish were still growing at 7 years upon an approximately linear scale. The ability to continue growth may depend on attaining a size which makes it possible to prey on smaller fish. Long-lived fish such as pike certainly continue to grow measurably for very long periods (Schloemer, 1936) but the increase in size is associated with an

increase in the size of the prey taken (Frost, 1954). Ricker (1945) comments that 'senile death is an everyday occurrence' in population-studies of the Indiana sun fish. This conclusion is, how-

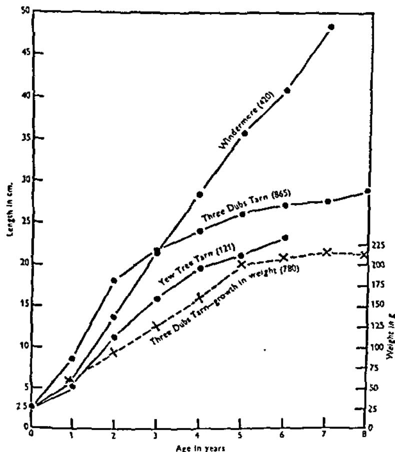


Fig. 16.—Growth of trout in Windermere and the small tarns (Frost and Smyly, 1952)

ever, based upon the failure of known sources of death (disease

But in many unfished populations of other species there is a steady increase in mortality with increasing age and size (Ricker, 1948).

A great deal of important information upon fish growth was collected by Schmalhausen (1928) from the data of a number of Russian workers (e.g. Tereschenko, 1917). In the sturgeon, growth continues actively throughout at least 30 years of life, with little decline in rate at sexual maturity (about 15 years). In the bream, on the other hand, the growth constant shows a more regular and progressive decline. These fish were found to mature at about 3 years, and degenerative changes in the

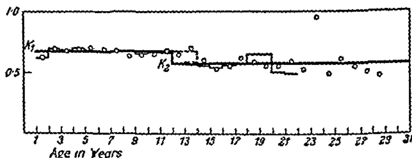


FIG. 17 (*a*).—Growth-constant for growth in length of the sturgeon, *Acipenser stellatus*, at various ages. Broken line—females: single points—males: thick line, mean value for males; dashes, mean value for females. $K_1 = 0{\cdot}67$, $K_2 = 0{\cdot}58$ (from Schmalhausen, 1928).

gonad were usually evident from the sixth year on—two definite stadia could be observed in the growth curve, one following puberty, and the other following this gonadal senescence, the growth coefficient settling down to a steady value thereafter without further decline up to 13 years of age (Fig. 17*a*, *b*, *c*). This rather closely resembles the pattern reported in the goldfish.

In *Xiphophorus* and *Lebistes* the male exhibits sharp specific size, but the female may continue to grow measurably throughout life, the pattern of growth differing little from that of the plaice (Wellensieck, 1953). Yet in these forms previous experience suggests that there is no striking difference between the survivals of the two sexes in captivity (Bellamy, 1934). In *Heterandria* both sexes reach a virtual limiting size (Wellensieck,

1953), Fig. 15*a*, *b*. In the goldfish, according to exhibition breeders, fertility reaches a maximum under aquarium conditions in the third year of life, declining thereafter, and almost all fish are sterile by the seventh year. Breeding at 10 years is recorded (Hervey and Hems, 1948). When the reproductive

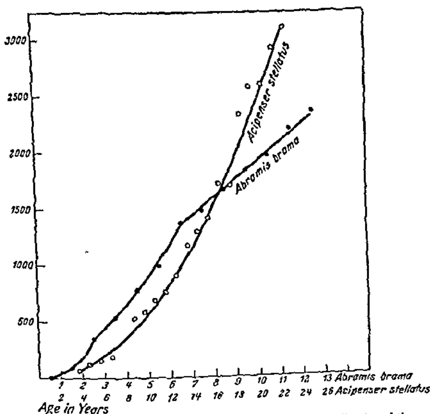


FIG. 17 (*b*).—Growth in weight of the sturgeon (*Acipenser stellatus*) and the bream (*Abramis brama*). Scale for *A. stellatus* 1 Russian lb = 100. Scale for *A. brama* 1 g. = 1 (after Schmalhausen, 1928).

life is over, however, the fish may improve greatly in condition, and appear much less sensitive to environmental damage than before. In exhibition fish the life-span appears to be about 17 years, though much older examples are known. The extreme

record of longevity appears to be between 30 and 40 years. Rate of growth is extremely variable. One specimen, kept in a six-gallon tank, reached a length of only 4 inches in 25 years (*Hervey and Hems, 1948*).

In none of these cases is it clear how large a part of the potential life-cycle is actually covered by the observed growth curve. In most fish the rate of growth does in fact decline with age, though in many the effective reproductive life appears to

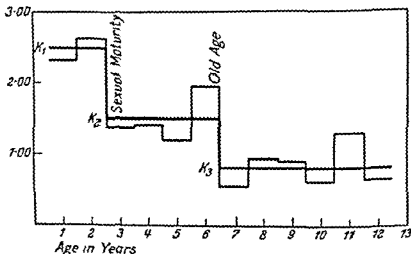


FIG. 17 (*c*).—Growth in weight of the Bream (*Abramis brama*)—annual increments. The mean growth-coefficients at various stadia (youth, maturity, postreproductive life) are indicated by transverse lines $K_{1, 2, 3}$ (from Schmalhausen, 1928).

have ceased long before this decline has produced an almost stationary body-size. The reproductive decline, moreover, does not appear to involve any decrease in vigour, and may actually imply the reverse, in view of the hazards which reproduction involves for many fish.

In the small teleosts, it ought to be possible to answer most of these questions by direct experiment. For this purpose the guppy (*Lebistes*) is proving a particularly suitable experimental animal, both because of the ease with which it can be reared and handled for purposes of measurement, and because of the

neatness with which its growth can be controlled by varying the food intake and living space.

A large population of *Lebistes* has been kept at University College under conditions in which each individual was isolated throughout life, and the dates of birth and death were accurately known. Dr. H. Spurway has kindly allowed me to use her data on this population; from these, and from fish which I have kept myself, it has been possible to construct a number of life-tables for *Lebistes* under different conditions. These are consistent, and all show a progressive increase in mortality with

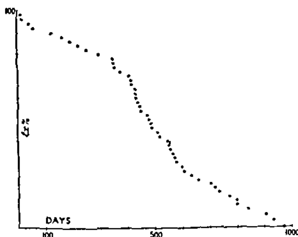


Fig. 18*a*.—Survival of 12 male and 40 female guppies (*Lebistes reticulatus*) kept individually at 25° C.: sexes combined. (From data provided by Dr. H. Spurway.)

advancing age very similar to that found in mammalian life-tables (Fig. 18*a*). The fish in this sample were not measured during life, but had certainly reached or exceeded the usual 'specific size'. The growth rate of female *Lebistes* and the size at which the growth curve reaches a plateau can very easily be altered. Spurway has found that these fish could be kept in individual half-pint milk bottles—by combining restricted space with restricted diet, I have kept female *Lebistes* at a length of about 2 cm. for as long as 600 days. In this state they are

reproductively mature (unlike the rats subjected to retardation by McCay—p. 149) and capable of resuming growth. There are 'specific sizes' characteristic of each size of container and each level of nutrition—or, alternatively, of each population-density in a tank, when a fish is promoted from one such container to a larger, or when fish are removed from a tank population, a new plateau is rapidly reached. The curve given by Wellensieck represents only one such equilibrium, The growth capacity also appears to decline somewhat throughout life, and there is a

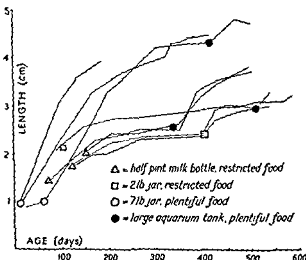


FIG. 18*b*.—Growth of female guppies (*Lebistes reticulatus*) in different conditions of feeding and living-space. The symbols indicate the time of transference to new conditions. All the fish were alive at the time of drawing. The growth pattern of the fish whose life-table is given in Fig. 18*a* approximated to that of the fastest group shown in this figure.

practical limit, as might be expected, to the size of guppy which can be produced at maximum food intake and maximum living space. The combination of variables in *Lebistes*, and the fact that the life-span of the non-growing males is not, upon present data, grossly different from that of the growing females, suggest that a great deal about growth and senescence in fish can be

learned by the collection of actuarial data for guppies subjected to different programmes of growth: this work is in hand, but it is in the nature of the subject that life-table making cannot be hurried, and life-tables under various conditions of growth were not ready for inclusion here. The growth curves shown in Fig. 18*b* are instructive, however, when we compare them with the closely similar growth-behaviour and pseudospecific size of wild trout.

It seems probable that there is as much variation in 'senescence' as in growth-patterns among teleosts. Some forms apparently resemble monocarpic plants, mortality being linked to reproduction. Some, in captivity, have a life-span determined by senescence, their mortality increasing with age on a curve closely similar to that of mammals. Some forms, however, may conceivably have an effectively indeterminate life-span, and are not at present known to undergo any form of senescence, reproductive or general, other than the accumulation of injuries, though this may well mean only that their 'determinate' maximum, as in wild birds, comes so late in relation to mortality as never to be reached in practice. The effect of variation in the growth-rate upon the development of senescence has yet to be determined.

2·4·2 REPTILES

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early growth depends on environmental conditions, being sometimes very rapid, and growth rate declines with increasing age, there are a number of forms where both sexes have an effective specific size which is reached early in life, and after the attainment of which no further growth occurs. The cessation of growth in these forms is apparently as definitive as that in mammals, and its timing does not appear to depend on the arrival of sexual maturity. There appears to be no close correlation between either of these two patterns of growth and the length of the life-span.

Among chelonians, both patterns of growth are known to occur. Continuous growth as a decreasing rate appears to be general in tortoises, the large species having inherently higher growth rates throughout. Townsend (1931, 1937) found that early growth in 100 specimens of the large *T. vicina*, kept in captivity, was potentially very rapid, and continued after the age of sexual maturity (about 20 years of age). Flower (1945) observed continuing growth in a 39-year old specimen of *T. graeca*. The age of sexual maturity in the male *Terrapene carolina* appears to lie between 12 and 15 years (Nichols, 1939). All these are known to be long-lived forms. On the other hand, the majority of terrapins exhibit specific size. In *Emys* Sergeev

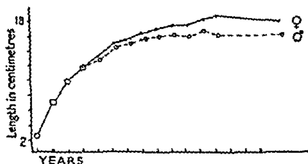


Fig. 19.—Growth of *Emys* (Sergeev, 1937).

(1937) found that growth-cessation by the fifteenth year of life was as complete as in the adult mammal (Fig. 19) although *E. orbicularis*, like *T. graeca*, is apparently capable of living 70–120 years and probably of breeding throughout life (Flower, 1937). Rollinat, however, on whose observations Flower's records were based, considered that growth in this form might continue for 30–40 years (Rollinat, 1934). Hildebrand (1932) studied the longevity and growth of over 1,000 specimens of *Malaclemmys centrata* in captivity—an investigation which is the nearest published approach to a chelonian life-table, but which was unfortunately continued in detail for only 10 years. He found the age of maturity much more variable than in mammals, some individuals being full-grown in 8–9 years, others requiring 12–15. The oldest specimens in captivity were 21 years old, and

'showed every appearance of being young animals', but other wild specimens taken when full-grown had been kept for 20 years without decline of vitality or reproductive power. Hildebrand placed the maximum life-span for this species at 40 years or more, but evidence from other small terrapins suggests that this may be a considerable underestimate. Although the only aquatic species which is known to have reached an age comparable with that of the land tortoises is *Emys orbicularis*, it would be very difficult to argue upon the existing evidence that specific size and determinate age are correlated in chelonians. Contrary to Bidder's hypothesis, specific size here seems to be an adaptation to carnivorous life in small pools, while continuing growth is found in land tortoises and marine turtles (Parker, 1926, 1929).

Crocodiles have also been credited with indeterminate growth —'Crocodili perhibentur esse admodum vivaces, atque grandescendi periodem itidem habere insignem; adeo ut hos solos ex animalibus perpetuo, dum vivunt, grandescere opinio fit. . . . At de aliquo testaceo genere, nihil certi, quod ad vitam ipsorum attinet, reperimus' [1] (*Hist. Vitae et Mortis*). Claims of longevity are based on the exceptional size of some specimens. Large alligators have been observed in captivity to remain for 25 years in a non-growing state, e.g. *Alligator sinensis* (Dathe, 1935), though the difficulties of accurate length-measurement are evident.

2·5 *Distribution of Senescence in Invertebrates*

Among invertebrates not only is there a demonstrable variety, greater than in vertebrates, in the nature of the preponderant senile process, but we have also the full range, from indeterminacy to very sharply defined determinacy of life-span. The gaps in our knowledge of life-cycles are so large that we cannot yet picture the distribution of senescence in invertebrate phylogeny: papers entitled 'The life-history of . . .' only very exceptionally include reference to the senescence of the species

[1] 'Crocodiles are held to be very lively, and to have a notable span of growth—so that they alone of beasts, so opinion runs, grow so long as they live. . . . But of any hard-skinned beast, as pertaining to their length of life, we find nothing certain.'

under study—an extraordinary deficiency, which is a measure of the equally extraordinary lack of interest in age processes. It is fairly evident, however, that the distribution both of senescence in general and of any one process of senescence, such as depletion or mechanical deterioration, is quite discontinuous in phylogeny. This evolutionary discontinuity is what we should expect if 'exhaustion of programme' is the common basis of adverse age changes.

Senescence in some shape or form probably occurs in every group where the power of regeneration or fissile reproduction is less than total, or where body-cells are not continuously and 'indeterminately' replaced. Some forms which 'degrow' under adverse conditions appear to be capable, in all probability, of unlimited alternate growth and degrowth, at least in the laboratory, while in a few, such as actinians, the adult can remain indefinitely in *statu quo*, though with a changing population of cells. Senescence is most striking in forms such as rotifers where determinacy of cell number is very highly-developed and the power of regeneration is usually negligible. There do not appear to be any invertebrate cells (except possibly pelecypod neurones, of whose longevity and renewability we know little) which are called upon to remain for 100 or more years in active function, like a human neurone, or for still longer, like the neurones of the tortoise. The distribution of senescence in invertebrates suggests that in spite of the general argument against the selection of long-lived forms, relatively great longevity is sometimes an evolved adaptation, and that if some cold-blooded vertebrates are in fact immune to senile change, that, too, is likewise a specialized mechanism and not a primitive or an 'inherent' mechanism which has been lost with increasing somatic complexity.

2·5·1 PORIFERA

Bidder infelicitously cited 'the sea anemone, the bath sponge and the water-vole' as three organisms insusceptible to senescence. The only serious study of senescence in Porifera appears to be that of Arndt (1928) who concludes that it does not occur, although some sponges are fatally disrupted by their own larvae. Aquarium specimens have an effectively limited life, as in so

many other groups, but sponges seem ideally able to conform to Bidder's expectations of them.

252 COELENTERATES

In hydromedusae, Child (1918) observed a progressive decrease in metabolism and pulsation rate with increasing size, which he regarded as evidence of senescence. His work on the processes of ageing and rejuvenation in hydroids (1915) depends on the criterion of resistance to cyanide as evidence of 'physiological age'—one which is hardly acceptable in this context. Child's results with *Pennaria*, using this test of age, were in any case less consistent than those he obtained with planarians, where cyanide resistance rose steadily throughout life (Child, 1915).

Evidence that the life-span of sea anemones is 'indeterminate' is probably stronger than for any other metazoan group. Dalyell's (1848) celebrated specimens of *Actinia* lived for 70 years in captivity without any sign of deterioration. An even more famous batch of sea anemones were collected 'some years prior to 1862', and were first identified as *Sagartia troglodytes* by Ashworth and Annandale (1904), later by Stephenson as *Cereus pedunculatus* (1935). They remained in the aquarium of Edinburgh University Department of Zoology until 1940 or 1942, when they were all simultaneously found dead. Budding continued freely throughout life, and the animals underwent no obvious change during eighty to ninety years of continuous observation (Warwick, 1954, personal communication). Whether gametogenesis likewise continued throughout life is not known.

Hydra. The long-standing controversy over the senescence of *Hydra* illustrates some of the difficulties of placing a gerontological interpretation on life-tables and histological appearances. *Hydra* was a favourite organism, earlier in the century, in the argument over the 'potentielle Unsterblichkeit' of metazoa. Differences in culture conditions almost certainly account for the very irregular results obtained.

Early workers (Hertwig, 1906; Boecker, 1914; Berninger, 1910) on this question found it impossible to keep *Hydra* for long periods without the onset of 'depression', evidenced by cloudy

swelling and cytolysis. With better cultural methods Goetsch (1922, 1925) kept individuals of *Pelmatohydra oligactis*, *Hydra attenuata*, and *Chlorohydra viridissima* alive for 27 months. Goetsch considered that like the actinians *Hydra* was capable of remaining indefinitely *in statu quo*. Gross (1925) working with *P. oligactis* failed to keep any individual alive for more than 349 days, 'senescence' being evidenced by irregular and hypertrophic budding or by the animal becoming smaller and smaller in the presence of abundant food. 'Senile' changes in Gross's material began after the fourth month of life. A life-table, drawn from Hase's (1909) data by Pearl and Miner (1935), extending over only 148 days, indicates some increase in mortality with age, but is closer to the log-linear than to the rectangular contour (see Fig. 6*c*, p. 20). Hartlaub (1916) had already described experiments on Syncorinae in which he concluded that the power of producing gametes was lost relatively early in life, while that of budding persisted.

David (1925) kept isolation records in cultures of *P. oligactis* and satisfied himself that in this form the individual animals tended to die between 20 and 28 months in approximate order of individual age—an important observation which has not been repeated. According to Schlottke, however (Schlottke, 1930), the material in David's histological sections was heavily parasitized. Schlottke's own observations suggested that all the tissues of *Hydra* are continuously replaced throughout life, from a subjacent reserve of interstitial cells. [illegible]

rejected at the base: a case, in other words, of 'indeterminate growth' coexisting with a final specific size.

In colonial hydroids, however, it seems to have been shown beyond reasonable doubt that the life [illegible]

the hydranth shrinks, the gut becomes filled with cellular debris, and the degenerating material is returned to the colony by the contraction of the hydranth itself. In *Obelia* and *Campanularia* Crowell (1953) has now shown that regression takes

place strictly in order of age, each hydranth having a life of 4 days at 21° C. and 7 at 17° C. When regression is accelerated by starvation or adverse culture conditions, the age order is still preserved.

2·5·3 SUNDRY INVERTEBRATES

Existing observations are scattered rather thinly over a number of groups. Child (1911, 1913, 1914, 1915, 1918) carried out exhaustive studies upon the regeneration of planarians, and upon their capacity for de-differentiation, to which subsequent research has been able to add little or nothing. Here again, as in *Pennaria*, he employed the increase in resistance to dilute cyanide solutions as a criterion of senescence, on the assumption that this change reflected a decrease in metabolic rate. While susceptibility decreased as a function of age in the growing animal, planarians kept for several months at a constant size showed no such increase, and planarians undergoing shrinkage under adverse food conditions showed a decrease in susceptibility. Child also demonstrated the 'rejuvenation', partial or entire, of regenerating fragments of planarians. This further observation, using the same criterion of resistance to toxicity (1915), that a gradient of 'rejuvenation' exists in *Stenostomum* (Rhabdocoela) during the production of new zooids has been confirmed by Sonneborn (1930) using direct life-table studies. Sonneborn's experiments showed that the regenerative effects of fission were markedly unequal in the two halves, since the head portions, which required only to regenerate tails, underwent typical senescence, and died after a limited number of divisions, while tails, which required to regenerate most of the body and nervous system, could be propagated indefinitely.

In *Aeolosoma* (Oligochaeta), Haemmerling (1924) found that the anterior end of the body appeared to undergo eventual senescence, new worms being produced from the posterior end. Stolč (1902) had already given a circumstantial histopathological account of 'senile' death in *Aeolosoma* as a whole, but the appearances observed might have resulted from almost any environmental cause. In *Nais* (Annelida), Stolte (1924, 1927) found extensive histological changes with age, with disappearance of the normal zones, degeneration of the visceral ganglia,

and the cessation of reserve-cell production from the embryonic tissue persisting in the posterior end. The significance of these changes is again obscure, and no attempt was made to determine actuarially the mortality rates at different ages. Rhabdocoelians have (Bresslau, 1928–33) been observed to be increasingly susceptible to protozoan parasites the longer they live.

How far the capacity for 'degrowth', which is found in planarians, is evidence of a potentially indeterminate life-span is not evident, but it seems likely that forms such as *Lineus* (Nemertinea), which revert on starvation over a period of years to a mass of cells resembling an embryo (Dawidoff, 1924), might be maintained indefinitely in alternate growth and degrowth until the patience of the investigator was exhausted.

The evidence in fissile worms at present suggests that nonsenescence depends upon fairly active replacement of cells, and that any organ which fails to take part in the regenerative process is liable to undergo senile change. Harms (1949) considered that the senescence of Serpulids was due primarily to changes in the nervous system, and rejuvenated old specimens of *Protula* by grafting young heads. Some further work on this subject as careful as that of Child and Sonneborn would probably be well worth undertaking.

Morphogenetic loss throughout life of the power of regeneration in a nematode of determinate cell-number was actually demonstrated by Pai (1928) in *Anguillula aceti*. Amputation of the tail with nuclear removal kills the animal at any age. In young individuals, provided the nucleus is left intact, wound healing and cytoplasmic regeneration can take place. In mature animals there is wound closure but no cytoplasmic regeneration, while in senile animals amputation is fatal. In *Anguillula* senescence follows a pattern very similar to that of rotifers (see below) and occurs at about 44 days. The degenerative cellular changes in ovaries, gut and nerve cells have been described: these appear in the two or three days preceding death Pai, 1928; Bürger, 1954).

2·5·4 ROTIFERS

The ageing of rotifers is one of the most spectacular examples of endogenous senescence in animals. It is also one of the most

thoroughly-studied, at least from the descriptive point of view. The life-span varies in different species from a few days to several months, and each species tends to exhibit very sharp specific age. After a period of growth, which takes place by increase in cell size, the nuclear number being fixed, and adult vigour, rotifers enter a period of senescence, with conspicuous loss of activity, degeneration of cells, deposition of pigment, and ultimate death in extension. In some forms the senescent phase is genuinely post-reproductive, but in the majority it occurs while egg-laying is still occurring at a diminished rate, and may be accompanied by the production of malformed eggs, or eggs of varying size.

The external appearances of rotifer senescence have been vividly described in several forms (*Callidina*, Plate 1886; *Pleurotrocha*, Metchnikoff, 1907; *Proales*, Noyes, 1922; Jennings and Lynch, 1928; *Hydatina*, Plate, 1886; *Lecane*, Szabó, 1935; Miller, 1931; *Rotifer vulgaris*, Spemann, 1924). The animal becomes sluggish in behaviour and reaction to jarring, the tissues and cuticle shrink and become opaque or granular in appearance, swimming is replaced by creeping, pigment accumulates in the gut, digestive gland and mastax. The movements of the pharyngeal cilia are the last signs of life to persist.

It seems clear that this is an endogenous process of degeneration. A number of attempts have been made to correlate it with other features of rotifer organization. Plate (1886) considered that senescence in *Hydatina* occurred typically when the activity of the ovary, and the supply of germ cells, failed. This is not the case in all rotifers, however. In *Lecane inermis* Miller (1931) found that the mictic females cease egg laying early in life and have a relatively prolonged post-reproductive period, while amictic females show signs of age before the last egg is produced, and all are dead within two days thereafter; the life-span of males is even shorter (Fig. 20). In this species, fertilization of the mictic females does not appear to influence longevity. Miller attributes the difference in life-span between mictic and amictic females directly to the difference in fertility, but this is not fully borne out by her life-tables, the chief difference being in the longer post-reproductive period of the mictic females. In *Hydatina senta* it is the amictic females which are the longer

lived (Ferris, 1932). In both these species, however, the form having the higher reproductive rate in early life dies younger, an observation which ... results from ... until death (... *rotifers*, appears itself to be adversely affected by somatic senescence, the ... failing to enter the ... and of low ... 1928). Old ... *sordida* consist of two types of

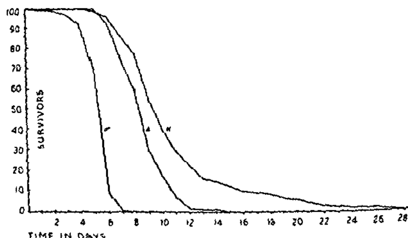


FIG. 20.—Survival curves for males, mictic (M) and amictic (A) females of *Lecane inermis* (from Miller, 1931).

senile individuals, some thick and opaque, and others abnormally transparent, with pigmentation of the gastric glands. There is considerable individual variation in the length of survival once senescence is established.

Impairm... ... the process, though in some ... it appears to be the digestive system which first deteriorates. The pattern is fully consistent with some or all of the somatic cells having a fixed survival-time under normal metabolic conditions—a highly important precedent for the study of other types of metazoan senescence. The senescent change

depends directly upon metabolism—encysted rotifers can survive for very long periods (59 years—Rahm, 1923) and display enhanced reproductive performance on emergence from diapause (Dobers, 1915).

It is particularly interesting that this dramatic senescence in rotifers accompanies a very strict determinacy of cell number, a lack of regenerative capacity, and in most species a very

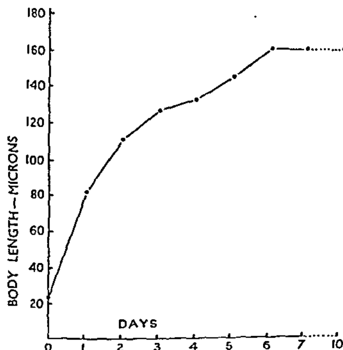


Fig. 21.—Growth in length of *Philodina citrina* (Lansing, 1948).

limited power of repair. Nuclear division after hatching has not been described in any rotifer. In many forms wound healing is [illegible]

of the coronal lobes can be regenerated, as can parts of the coronal funnel in *Cupelopagis* (Huhnerhoff, 1931; references from Hyman, 1951).

The somatic growth of rotifers has been studied by several workers. *Rotifer vulgaris* shows little or no change in size throughout life (Spemann, 1924). The growth curve of *Apsilus vorax* is a parabola, with shrinkage before death (Cori, 1925) while in *Philodina citrina* growth ceases by the sixth day (Lansing, 1948). (See Fig. 21.) Lansing also made the striking observation that

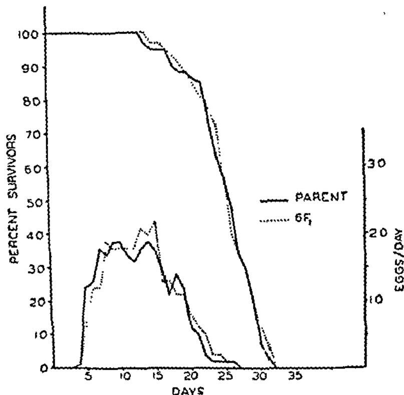


Fig. 22.—Life-span and egglaying of *Philodina citrina* (Rotifera) over 6 generations in normal culture (from Lansing, 1952).

if these rotifers are propagated in each generation from eggs laid at or after the fifth day of maternal life, the rate of development becomes progressively greater and greater from generation to generation, and the longevity of the individual less and less, so that clones propagated in each generation from old mothers invariable become extinct (Figs. 22, 23, 24). Jennings

and Lynch (1928) had already noted that the offspring of very old rotifers are less viable than those of vigorous adults. Lansing's results suggested that the effects of maternal age are cumulative from generation to generation: they were also reversible, the eggs laid by young members of such a clone being capable of giving rise to normally long-lived individuals. Lansing also found that clones propagated in each generation from the eggs of very young mothers showed an increase in

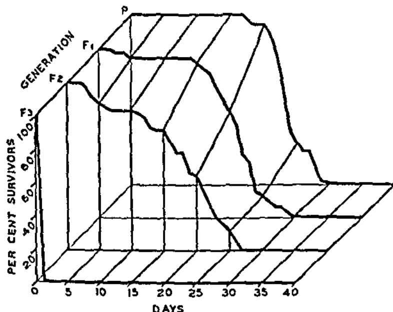


FIG. 23.—Progressive decline in life-span of a strain of *Philodina citrina* (Rotifera) raised in each generation from eggs laid by old mothers (from Lansing, 1952).

longevity over the control stock. In *Euchlanis triquetra*, the 'young' orthoclone could not be maintained, however, because within a few generations it gave rise largely to male-producing eggs. Lansing regards his ageing-factor as a product of growth- [illegible] the individual animal at the point [illegible] test. [illegible] ffecting the life-cycle of the progeny has been much studied in forms

which give rise periodically to mictic generations. The literature on sex-determination in rotifers is reviewed by Hyman (1951). The longevity of the two types of female differs considerably; 'somewhere in the ontogeny of the females, it must be determined which kind of egg they are destined to lay. The determination occurs during the maturation of the egg from which

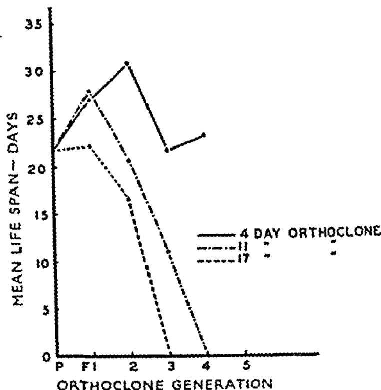


FIG. 24.—Life-span of successive generations of *Philodina* reared in each generation from the eggs of 4- 11- and 17- day-old mothers (Lansing, 1948).

the female comes, that is, during the last few hours before the egg is laid' (Hyman, 1951). Both internal and environmental factors of great complexity appear to operate in different forms. 'The conclusion from numerous researches seems to be that, in addition to an inherent rhythm as regards male production, monotony of conditions suppresses mictic females, whereas any

sudden change, especially of diet and of physiochemical composition of the water, induces the appearance of mictic females' (Hyman, 1951). The reason for the difference in longevity between Lansing's old and young orthoclones is not, it should be noted, entirely comparable to that between mictic and amictic females. It does not seem to represent a difference in specific age due to a shortening of that part of the survival-curves which, owing to the low early mortality in rotifers, is usually horizontal, but rather a 'breaking away' of this plateau by the introduction of a higher and higher early mortality, the curve becoming less and less rectangular and more and more oblique. If conclusions are to be drawn upon the effect of maternal age upon senescence, this difference is important.

It is possible that the uniform specific age of rotifer populations is due to *depletion*. Reproductive exhaustion has already been discussed. It is also known that the limited regeneration observed in *Stephanoceros* takes place at the expense of reproduction and of somatic growth. Little is known of the metabolic capacity of rotifers—they apparently store glycogen, but may be incapable of assimilating carbohydrate (Hyman, 1951). Sudden senescence might well represent the exhaustion of a metabolic substrate, or of a non-renewable system. *Accumulation* has also been suggested: pigment certainly does accumulate, probably secondarily to the ageing process. Lansing (1942) demonstrated the accumulation of calcium in old rotifers, and succeeded in prolonging their life by immersion in dilute citrate solution—it is not clear how often this process can be repeated. A more curious factor influencing the life-span was observed by Edmondson (1945) in *Floscularia conifera*, where individuals growing in aggregation reach twice the length, twice the age, and a higher level of fertility than solitary specimens.

The peculiarities of rotifer organization are so numerous that some, if not all, of the mechanisms controlling their longevity are likely to be peculiar to the group. On the other hand, their short life-span makes them a suitable object for study, and they provide an unequivocal example of senescence coupled with cellular non-renewal which calls for further investigation.

2·5·5 ARTHROPODS

Senescence in arthropods is widespread and probably universal. Those forms which have wings, jaws, bristles, and other chitinous tegumentary structures not renewed by moulting are particularly liable to genuinely 'mechanical' senescence. In the forms which moult as adults, the time of ecdysis is a particularly arduous one, judged by the mortality, and many of these, such as *Daphnia* and large spiders, appear very often to die in the attempt to carry out a final moult.

'Physiological' senescence, in the sense in which nineteenth-century biology used the term, also appears in a convincing form for the first time in arthropods, since, as Metchnikoff first pointed out (1907, 1915), a non-feeding imago *must* be regarded as expendable from the evolutionary point of view. The evolution of short sexual life as a modification in some groups is balanced by the evolution of a very long sexual life in specialized individuals of other, social, species, as part of the adaptive development of a group-existence—the longest life-span being reached in one or both sexual forms among true ants and termites.

There is no known case of arthropod indeterminacy comparable with that of actinians. Growth in most insect imagines is more or less rigidly limited, although the capacity for continued cell division persists in varying degrees. According to Harms (1949), somatic mitosis in many arthropod imagines is virtually confined to the mid-gut. Mitotic capacity has not been shown to bear any relationship to longevity, except perhaps in forms producing queens, where the relation of continued reproduction to long life might be either a direct example of cause and effect, or the result of two parallel adaptations. Some solitary arthropods are capable of very long life (20 years in tarantulas, Baerg 1945, possibly 50 years in lobsters, Herrick, 1896).

Crustacea. The small crustacea (Cladocerans, Copepods, Isopods) generally show very sharp specific age. In *Daphnia*[1] this

[1] There is a striking lack of unanimity in the literature over the 'normal' life-span of various species of *Daphnia*, even when grown in apparently similar media. Fritsch (1953) has shown that this variation depends to some extent upon the amount of available pantothenic acid. Where Daphnids are

appears to be definable in terms of instars, *D. longispina* living for 19-22 instars, the duration of which depend upon the conditions of culture (Ingle, Wood and Banta, 1937) and *D. magna* for 17 instars (Anderson and Jenkins, 1942). Detailed studies

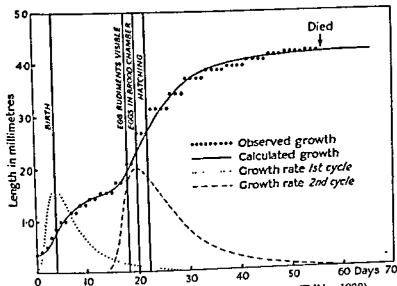


FIG. 25 (*a*).—Growth of *Daphnia magna*—first type (Edlén, 1938).

particular interest. Edlén (1938) showed that the growth of normal daphnids takes place in two cycles, the first levelling off after three or four instars, and the second coinciding with the development of the gonad. He found three types of pattern in

fed upon living cultures of protozoans or algae, the food organism itself may metabolize and remove pantothenic acid. It is highly questionable in view of Fritsch's findings how far the life-tables obtained by workers using ... or even by one worker at different times, are

the growth of individual *D. magna*. In the majority of specimens (Fig. 25*a*) the two cycles of growth followed one another, the growth-potential in the second cycle falling almost to zero with increasing age; this fall is accompanied by a decrease in egg size and number, and the animal finally dies after a short period in which growth has almost ceased. In individuals of the second

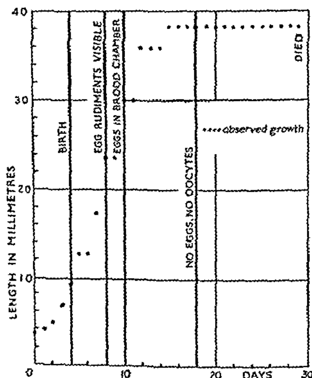


FIG. 25 (*b*).—Growth of *D. magna*—second type: growth-phases superimposed (Edlén, 1938).

type (Fig. 25*b*) the two growth cycles were superimposed—in these growth was very rapid, there was no prepubertal 'shelf' in the curve of body size, and fertility was lost early, although the life-span appeared to be normal. The third type (Fig. 25*c*) showed only the first cycle of growth, but no gonadal function developed, and adult size was not attained. These forms died early. Edlén considered that the developing ovary exerts a

hormonal control over growth, and possibly over the maintenance of life-processes generally.

The chief senile changes in *Daphnia* appear to be in the fat body, intestinal epithelium and musculature (Schulze-Röbbecke, 1951). This author found no evidence of the 'cerebral death' which was once widely accepted as the general cause of invertebrate senescence (Harms, 1926; Muhlmann, 1900, 1911), and which was described by Walter (1922) in *Cyclops*. Withdrawal

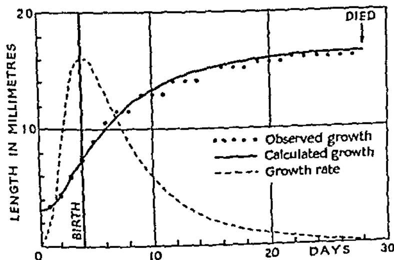


FIG. 25 (*c*).—Growth of *D. magna*—third type. One growth-cycle only (Edlén, 1938).

of ovarian activity does not seem to be the direct cause of senescence in *Daphnia*. Schulze-Robbecke's oldest specimens still showed considerable ovarian activity, and continued to lay eggs, though in reduced numbers, up to the time of death. Oocytes at all stages of maturation remained in the ovary to the last. Schulze-Röbbecke attributed the death of *Daphnia* in old age to failure of nutrition following degenerative changes in the gut.

Walter's work on *Cyclops* (1922) dealt with *C. viridis*, which has a life-span of about 9 months, 'senile' change in gut epithelium and in the cerebral ganglia being evident from the

fifth month. Somatic mitosis in adult life occurs only in the mid-gut of *Cyclops*, and in this region 'senile' changes were not found (Harms, 1949). The most striking degenerative changes in *Cyclops* were found in the chromatin of the ganglion cells, with the appearance of large inclusion bodies suspiciously reminiscent of virus inclusions or fixation artefacts, and in the antennules. Gut degeneration occurred later in life, about the [illegible]

with the process of senescence.

Needham (A. E. Needham, 1950) has studied the growth rate of limb regeneration in *Asellus aquaticus*; growth in crustacea, on Needham's figures for *Asellus* and *Carcinus*, is determinate and the curve sigmoid, the arithmetic rate of growth rising to a maximum and declining asymptotically thereafter to zero. The geometric rate of growth declines monotonically with age from the outset, and the rate of decline itself declines with increasing age. The specific regeneration rate decreases progressively with age, owing to the progressive increase in the duration of each instar; the rate of decline is much less than that of the normal growth rate, and itself declines with age. 'In some crustacea the limiting size is attained at an age beyond the mean expected life-span. Growth is indeterminate in Crustacea only in this sense. They are not potentially immortal.' This investigation illustrates once again the difficulty of characterizing the growth-behaviour of real organisms mathematically: the decline of arithmetic growth may be asymptotic, or tangible size increase may continue; in crustacea there is the additional difficulty that growth is discontinuous, being interrupted by stadia, which superimpose a 'quantal' effect on the smooth ideal curve. The conclusion of Needham's studies is that the growth of crustacea follows a convergent series, and must cease, presumably, for practical purposes in any form which lives long enough. But the relation between such cessation and determinacy of life-span is still entirely conjectural.

Insects. It has long been recognized that several separate types of senile change may occur in insects. Mechanical damage

to the cuticle (Blunck, 1924; Wigglesworth, 1945), depletion of reserves both in f [illegible]
in some cases by [illegible]
1953), accumula [illegible]
ation of the nervous system (Hodge, 1894–95; Pixell-Goodrich, 1920; Schmidt, 1923; Weyer, 1931, etc.) and 'general senile decay' have all been demonstrated by more or less satisfactory evidence. The vast majority of holometabolous [illegible]

seems, however, to vary widely, but they have the common property of being processes operating in a cellular system where little or no renewal, and no further morphogenetic development, are occurring.

One of the best general descriptions of insect senescence is given by Blunck (1924) for *Dytiscus marginalis*: he describes the main signs of advancing age as diminution in activity and deterioration of the epicuticle, with the growth of colonial protozoa on the dorsal shield, legs and mouth parts, which the animal cannot any longer clean effectively. The cleaning secretions seem to be reduced, and the chitin appears brittle, whole legs or antennae being occasionally snapped off in swimming. If pygidial gland secretion fails, air enters the subalar air chamber and the beetle drowns. In the beetles dissected by Blunck, the gonads had almost disappeared during the third year of life, the fat-body was increased in size, almost filling the body cavity, but chalky and full of concretions. In some individuals there was almost complete atrophy of the wing muscles. The extreme life-span is under 3 years, females living longer than males: sexual activity usually ceases in the second year but may persist in individuals into the third. A number of senile processes, which may not be mutually dependent, can be detected in this description. The balance between mechanical, depletive and 'morphogenetic' senescence must vary considerably from species to species, and even from individual to individual. Blunck's description is of interest in providing not only an account of such a mixed senescence, but one of the very few instances where the 'change in inert structures', so popular with colloid

chemists investigating senescence, really seems to occur—in the progressive hardening and weakening of the chitin of *Dytiscus* elytra, which Blunck found to be a reliable rough measure of the age of specimens taken in the wild. On the other hand, a considerable part of this change, as Blunck himself suspected, may represent failure to secrete the normal lubricant coat—a cellular rather than a mechanical deterioration.

In many insects, especially lepidoptera, there is evidence that the fat-body contains a definite reserve of materials, which are not replaceable during imaginal life. In females of the moth *Ephestia elutella*, longevity and fecundity are both functions of body weight at eclosion (Waloff, Norris and Broadhead, 1947). Longevity is also greater in virgin females, possibly owing to the sparing of reserves through egg-rudiment resorption (Norris, 1933, 1934). Exhaustion of the fat-body is characteristically found in *Ephestia* which appear to have died of old age. Norris (1934) found evidence that the fat-body contains two types of store, one needed for the maintenance of the ovaries and the other for the maintenance of life. The second appears to be supplemented by feeding the imago, but not the first (Norris, 1933). Similar deterioration of the fat-body has been described as a sign of senescence in *Carabus* and *Drosophila* (Krumbiegel, 1929) and *Sitodrepa panicea* (Janisch, 1924) in which the period of depletion is apparently hastened by exposure to CO_2. This type of 'depletion senescence' is, in fact, in one sense an extension of morphogenetic senescence, if in the transition from larva to imago the organism loses the power of synthesis or assimilation of some material which it is able to store during larval and pupal life. How far depletion of larval reserves is a general feature of insect senescence it is difficult to say. The non-feeding or the starved imago is necessarily dependent upon what stores it has, although Metchnikoff (1915) from a careful study of *Bombyx*, favoured an 'accumulative' rather than a 'depletive' mechanism to account for imaginal death. Other imagines probably vary a great deal in their biochemical accomplishments. Some lepidopteran imagines feed on nectar and are known to absorb water and sugars. Frohawk (1935) kept *Nymphalis antiopa* alive for three months from eclosion by feeding sugar solution. On the other hand, robust Coleoptera, such as *Blaps*, are fully

n years, while
much longer.
greatly pro-
longed the life of butterflies by decapitating them.

The influence of reproduction on life-span is equally variable, but it often seems to involve inroads upon stored and irreplaceable reserves. Unmated females of *Periplaneta* lay fewer eggs than mated females and live longer (Griffiths and Tauber, 1942). The life-span in both male and female *Drosophila* is substantially decreased by mating (Bilewicz 1953). Krumbiegel

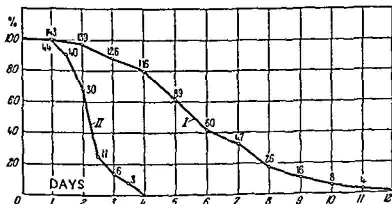


Fig. 26.—Survival curves of 145 isolated virgin females (I) and 44 isolated, fertilized females (II) of the moth *Fumea crassiorella* (from Matthes, 1951).

found that the reserves in the fat-body of Carabids decreases after first copulation, but increases again with feeding (1929). In the moth *Fumea crassiorella* Matthes (1951) found that the longevity of the female was halved by copulation if egg-laying was allowed, and slightly reduced by it if egg-laying was prevented (Fig. 26).

The theory of 'cerebral death' (*Gehirntod*) in insects arises chiefly from some long-standing work on bees. Hodge (1894, 1895), Pixell-Goodrich (1920) and Schmidt (1923) all described

According to Hodge, the cell-number in the brain of old workers was reduced by three quarters. Pixell-Goodrich found that in diseased, and therefore inactive, workers, the cerebral architecture was more normal than in healthy workers. Schmidt attributed the reduction in cell size and cell-number to direct 'wear by use', the amount of work done by the insect being a fixed quantity. Holmgren (1909) found a similar deterioration in the supraoesophageal ganglia of old termite primaries: the brain of old physogastric queens of *Eutermes* was reduced to two thirds of the volume usually found in virgin queens. Another instance of '*Gehirntod*' in insects was described by Hansemann (1914) in *Bacillus rossi* (Phasmidae).

Quite apart from the fact that they have been indiscriminately transferred to mammals, these findings themselves have been open to intermittent criticism.[1] Smallwood and Phillips (1916) were by no means satisfied that the changes in relative nuclear size described by Hodge in worker bees resulted from [illegible]

after evident deterioration in other organs. In a 5-year-old queen, Pflugfelder (1948) found some disturbances of cerebral histology especially in the corpora pedunculata, but no significant cerebral change in old drones and workers. Rockstein (1950), however, found a decline in cell-number in the brain of worker bees from a mean 522 at eclosion to 369 at 6 weeks. The complex behaviour of worker bees deteriorates suddenly just before death, moreover.

[illegible] of [illegible] of [illegible] evident in gut and musculature. 'Vielleicht hat v. Hansemann bereits töte Tiere untersucht, was sehr leicht vorkommen kann, da bei den Stabheuschrecken infolge ihrer Reaktionsträgheit der Übergang von den letzten Lebensaüsserungen zum Tode nicht ohne weiteres festzustellen ist.' The amount of senile change described either as a result of fixation-artefacts or the

[1] The large literature of neurone loss with increasing age in mammals, especially in the cerebellum, is reviewed by Andrew (1955).

sectioning of 'that which dies of itself' has yet to be assessed in the literature.

A considerable amount of work has been done upon the physiological factors which influence longevity in worker bees. Winter bees are known to be considerably longer-lived than the summer brood even when they are kept under similar conditions of temperature and activity. Maurizio (1946) found that caged winter bees had a mean survival of 36 days from eclosion compared with 24 days in caged summer bees. The life-span of summer bees can be prolonged in two ways—by feeding pollen to caged bees (Maurizio, 1946), or by removing all the sealed brood regularly from the colony, so that the same bees continue with brood-rearing throughout life—under these conditions bees may live as long as 72 days (Moskovljević, 1939; Maurizio, 1950).

Two factors appear to influence the longevity of workers. One of these is certainly activity. Ribbands (1950) found that anaesthesia with CO_2 had the effect of causing young bees to begin foraging earlier than usual: in bees which forage early, expectation of imaginal life is less (30·1 ± 1·2 days), but expectation of foraging-life is greater (15·0 ± 1·2 days) than in late starters (37·1 ± 0·6 and 10·8 ± 0·8 days). The second appears to be dietary. 'Winter bees differ from summer bees in the greater development of their pharyngeal glands and their fat-bodies. This development results from autumn consumption of pollen, in excess of the requirements for immediate brood-rearing. In queen-right colonies in summer, prevention of brood-rearing can produce similar consequences, and in pre-swarming colonies temporary interruption of brood-rearing produces conditions different only in degree.' In all these cases the increased expectation of life is associated both with enhanced development of t[illegible]

([illegible]

v[illegible]

[illegible] life can be increased [illegible]

of brood. There is also ground for believing that the activity of worker bees is reduced by the possession of internal food

reserves. In winter bees, then, absence of brood leads to repletion, which in turn induces both quiescence and inherently greater longevity at a time when both are beneficial to survival. The expectation of foraging life decreases in proportion to the age of the bee when it begins to forage—endogenous senescence therefore appears to play a part in limiting the life of workers, and they do not all die from accident alone (Ribbands, 1952). Whatever the facts concerning '*Gehirntod*', this process of senescence appears to contain a major depletive element, combined, in all probability, with an element of mechanical damage. In this respect the senescence of worker bees conforms to a pattern which seems to be widespread in insects.

2·5 6 MOLLUSCS

Pelseneer (1934) divides molluscs in the wild into annual species, pluriennial species with a short reproductive life, and pluriennial species with a long reproductive life. In some members of this last group, indeterminacy of life-span cannot be excluded. Most of the evidence is obtained from wild material. The combination of patterns appears analogous to that found in fish. Like fish, molluscs include short-lived forms, forms with a longer but apparently determinate life, and forms, expecially among the larger pelecypods, which appear to have no maximum size.

The annual forms include many nudibranchs (Pelseneer, 1934, 1935) and probably most of the smaller freshwater species (*Paludestrina jenkinsi*—Boycott, 1936; *Ancylus*—Hunter, 1953). According to Boycott (1936) *Planorbis corneus* is the only British fresh water pulmonate which is not normally an annual. Many of these annual forms die immediately after reproduction. In *Viviparus contectoides* (van Cleave and Lederer, 1932) and *V. bengalensis* (Annandale and Sewell, 1921) the wild males live one, and the females up to three years. In captivity Oldham kept male *V. contectus* for 4½ and female for 5 years (Oldham, 1931), and living embryos were present at the time of death. Growth, judged by length, ceased in the second or third year of life. A number of other forms live for a maximum of 2 or 3 years in the wild, breeding during one or two seasons (*Lioplax*—van Cleave and Chambers, 1935; *Bithynia*—Boycott, 1936;

Lilly, 1953; *Fossaria*—van Cleave, 1935; *Sphaerium*—Foster, 1932; *Teredo navalis*—Grave, 1928). Specimens of *Limnaea columella* kept in captivity under good conditions give a life-table showing a typical senile increase in force of mortality similar to that in *Drosophila* (Winsor and Winsor 1935; Baily 1931). The growth of *Limnaea* has been studied by Baily (1931) and Crabb (1929). Among rather longer-lived forms, Pelseneer (1934) found a complete cessation of shell growth and a decline

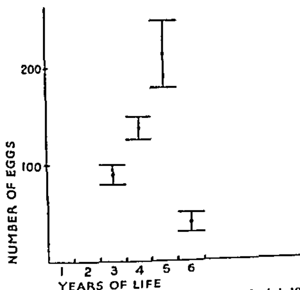


FIG. 27.—Egg production of *Eulota fruticum* (after Kunkel, 1928).

in fertility with age in *Gibbula umbilicalis*, complete infertility being general at about 54 months, and the extreme life-span [illegible] the relation of egg-laying to age [illegible] ith takes place [illegible] sted' (Kunkel, 1928). (Fig. 27.) In *Physa gyrina* DeWitt ([illegible]) found a distinct post-reproductive period, amounting to as much as 49 per cent of the total life-span in mass culture, or 36 per cent in isolation culture, the overall mean life-spans being 211 and 143 days respectively. Szabó and Szabó (1929–36 *passim*) published a

number of studies upon the 'senescent' changes observable in the digestive gland and nervous system of *Agriolimax:* these, however, were inconstant from species to species, and a life-table (Fig. 6*c*, p. 20) constructed from their data by Pearl & Miner (1935) shows a steady high mortality: it is probable that none of these slugs reached their maximum potential age.

Very little evidence exists to relate the apparent senescence of short-lived molluscs in the wild to their growth pattern, or to their potential life-span in isolation. Van Cleave (1935) and Hoff (1937) considered that the snails *Fossaria* and *Viviparus* continue to grow throughout life; in these forms, according to van Cleave, the maximum size which is characteristic of the facies of any colony is secured by a combination of environmental effects on the growth rate and an endogenous process of senescence which kills the animal after the completion of its life-cycle, irrespective of its general somatic growth. In the large *Trochus niloticus* Rao (1937) found no evidence of senile mortality, the upper limit of age being about 12 years in a wild population, and growth continuing at a decreasing rate throughout life. On the other hand, in spiral gastropods with an elaborate lip armature, growth must be *effectively* determinate so far as shell size is concerned. It has been suggested that in *Polygyra* growth in size ceases at lip-formation, but body weight and shell thickness continue to increase (Foster, 1936). Przibram (1909) quoted observations by Taylor and de Villepoix that the gland-cells of the mantle disappear in fully-grown specimens of *Helix aspersa, H. nemoralis* and *Clausilia perversa.* The growth of molluscs is seasonal, and the development of the gonad appears in some forms to compete with, or inhibit, body growth—in oysters, the periods of shell growth occur in each year before and after spawning (Orton, 1928) while in *Hydrobia ulvae* parasitic castration leads to gigantism (Rothschild, 1935). The life-span of such giants was unfortunately not recorded. On a small series of *Limnaea columella* Baily (1931) found that shell growth ceased at or soon after sexual maturity, and that the shortest-lived individuals were those with the highest growth rates. A life-table was constructed for this species by Winsor and Winsor (1935) (Fig. 28). Species whose life-cycle rarely exceeds two years may be capable of much

longer life in captivity. Oldham (1930) kept *Planorbis corneus* in active reproduction up to 6 years of age. Many Helicidae, especially the smaller forms, have been regarded as annuals in the wild (Lamy, 1933; Pelseneer, 1935): the potential life of helicids and medium-sized land snails in captivity (excluding diapause, aestivation and so on), may, however, reach or exceed 10 years (*Rumina decollata*, 12 years, '*Helix spiriplana*', 15 years—Vignal 1919; *Helix pomatia*, 6–7 years—Künkel 1916;

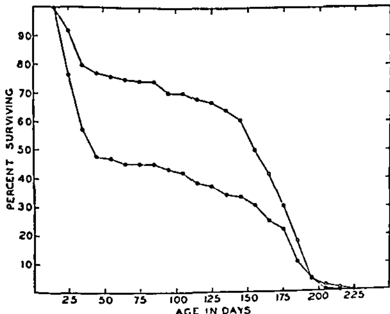


Fig. 28.—Life-span of the pulmonate *Limnaea columella* at two different population densities (from Winsor and Winsor, 1935).

6–8 years—Cuénot, 1911; *H. hortensis*, 6 years, hybrid *H. hortensis* × *nemoralis* 10 years—Cuénot, 1911) while *Oxystyla capax* has been revived from diapause after 23 years (Baker, 1934).

Even less is known about the longevity and liability to senescence of most marine gastropods. In *Acmaea dorsuosa* Abe (1932) found that growth continued in 15-year-old specimens from some localities, while in other localities an apparent specific size was reached at 5 years. Apparent specific size in certain

colonies was also found by Hamai (1937) in *Patelloida grata*. The most suggestive evidence of a determinate life-span in limpets comes from Fischer-Piette's (1939) observations which showed a definite inverse relationship between longevity, judged by growth rings, and rate of growth in different stations (Fig. 29). This strongly suggests that a process of morphogenetic ageing is occurring at different rates depending on the rate of growth.

In some pelecypods, there might be ground for regarding growth as genuinely indeterminate. It continues in the oldest

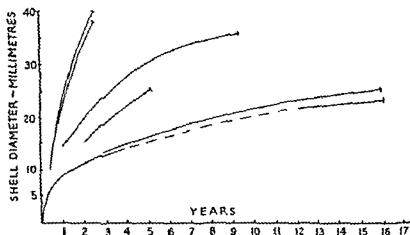


FIG. 29.—Growth and longevity of *Patella vulgata* in various stations, showing *the short life of rapidly-growing populations (from Fischer-Piette, 1939)*.

recorded specimens, and the occurrence of abnormally large individuals of species whose age can be estimated by growth rings makes it possible also to estimate the rate of decline of growth rate by measurement of the intervals between the rings. Growth continuing actively to the maximum recorded age has been found in many forms (*Cardium*, 16 years—Weymouth and Thompson, 1930; *Venus mercenaria*, 40 years—Hopkins, 1930; *Siliqua*, 14–16 years—Weymouth, 1931; *Pecten jessoensis*, 8 years—Bazykalova, 1934; *Mya*, 7–8 years—Newcombe, 1935, 1936). The larger fresh-water pelecypods, which have fewer enemies and are not subject to tidal disturbances, reach even greater ages. Huge specimens of the washboard mussel, *Mega-*

Ionaias gigantea (Unionidae) showing 54 and 36 annual rings are recorded (Chamberlain, 1933)—these molluscs were still growing, and even longer [illegible]

old to be followed for a further 15 years, and the correspondence of adult growth rings to years confirmed (Isely, 1931). (See also Coker, Shira, Clark and Howard, 1919–20.) In the small *Margaritana margaritifera* no important decline in the growth rate has occurred at 13 years (Saldau, 1939.) Geyer (1909) gave this species a life-span of at least 60 years. The estimate of 100 years quoted by Korschelt from Israel (1914) is unlikely but not impossible.

The supposed longevity of *Tridacna* has already been mentioned, together with the fact that nothing whatever is known about its real life-span. The same applies to many large marine [illegible]

The pelecypods also illustrate the risks of purely ideal and mathematical representations of growth-pattern. Pseudo-specific size from environmental causes is common. In *Siliqua* (Weymouth, 1931), some populations reach an apparent limiting size, cease altogether to grow thereafter, and die early: this, like Fischer-Piette's observation on limpets (1939) might suggest that a senile process is at work. Wild limpets apparently die while in active growth, but those which grow fastest die earliest (Fig. 29). Other molluscan populations have growth records which, though fitted for practical purposes to an asymptotic curve, actually give observed readings in the highest age groups which lie well above such a curve, and indicate that in these groups growth is continuing (Weymouth, 1931). There is an obvious objection to the use of growth rings to measure age, however, if conclusions are then to be drawn about continuing growth—arrest of growth lasting for years would leave no record of itself in this system of notation. The results obtained by the use of the ring method in pelecypods have so far been reasonably consistent (see Newcombe, 1936). The validity of growth rings as annual markers requires careful confirmation in each population examined, however (Haskings, 1954).

Hopkins (1930) found that in *Venus mercenaria* growth was continuing actively at 20 years. The oldest specimens aged by growth rings were in general not the largest shells. Some small examples had reached an estimated age of 40 years, and appeared to have grown abnormally slowly. This observation, like Fischer-Piette's (1939) and Weymouth's (1931) findings, should lead to a great deal of caution in regarding the life-span of any mollusc as indeterminate in the same sense as that of actinians.

2·6 *Senescence in Wild Populations*

Senescence as a potential part of the individual life-cycle is, as we have seen, widespread: in discussing the evolution of senile processes, however, it is important to know how far it really occurs in wild animals. The weight of evidence suggests that senescence in the wild is rare but not unknown. Its commonest form is undoubtedly the pseudo-senescence which follows reproduction, but genuine senescence analogous to that of man is occasionally reached, at least by individuals, while there are probably some forms in which it is normally reached. If our observation of animal life-cycles were confined to small birds and mammals in the wild, however, we should probably not recognize senescence as an entity except in ourselves.

2·6·1 VERTEBRATES

Although data from bird and small mammal populations have perhaps led to an overstatement of the case against 'natural' senescence, old age is undoubtedly a relatively rare or very rare termination to the life-cycle of vertebrates studied in the field—as it is for man in societies where medical and economic conditions are bad. For large numbers of animal species, the typical curve is one in which a high or very high infant mortality rate is succeeded by a high adult mortality rate which does not increase with age. These species, even when they are capable of senescence, never reach it. This type of curve has been repeatedly demonstrated in population studies, (see Lack, 1954). Whereas in voles kept in the laboratory the survival curve approximates to that of man (Leslie and Ranson,

1940, Fig. 30), in wild voles (Hinton, 1925, 1926; Elton, 1942) and in *Peromyscus* (Burt, 1940) senescence is never observed, judging from the state of the teeth and bones of recent and fossil animals. In some populations the vole must be regarded as an annual (Elton, 1942). Tooth wear is a reliable index of age in short-tailed shrews, those over 2 years of age being edentulous,

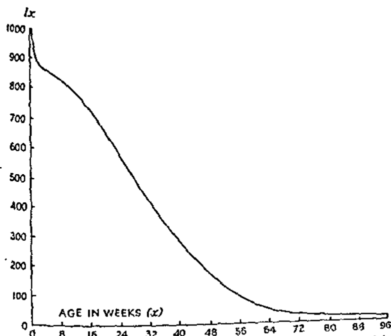


FIG. 30.—Smoothed survival curve for the vole, *Microtus agrestis* in captivity (from Leslie and Ranson, 1940).

but age limitation by this mechanical form of senescence is more potential than actual since few survive to exhibit it. They may survive in captivity up to 33 months (Pearson, 1945).

The log-linear pattern of decline in survivorship is highly characteristic of birds. It has been demonstrated in the blackbird, song-thrush, robin, starling and lapwing (Lack, 1943a, b, c), redstart (Buxton, 1950), American robin (Farner, 1945) and herring gull (Marshall, 1947). In a series of robins ringed by Lack (1943a), 111 out of 144 leaving the nest (77 per cent) died

in the first year. This compares with a maximum recorded age of 11 years, which is occasionally reached in the wild state. The succeeding annual mortality was at a steady rate approaching 50 per cent. A survivorship curve for lapwings (*Vanellus vanellus*) calculated from 1333 birds is closely fitted by a line corresponding to a constant mortality of 40 per cent per annum (Kraak, Rinkel and Hoogerheide, 1940; Lack, 1950). The rates of mortality for most birds which have been studied appear to fall between 30 and 60 per cent per annum. Very much lower figures have been recorded for large sea birds such as cormorants (Kortlandt, 1942) in which the mortality was found to decline from 17 per cent before fledging to an annual rate of 4 per cent between the third and twelfth years. The annual mortality in one species of albatross (*Diomedea epomophora*) is only 3 per cent. Such birds may well live to reach senescence, if their life-span is 50 years. But considerable evidence has accumulated, chiefly from ringing studies, to show that the expectation of life of some wild birds actually increases with age. Although the total of ringed birds recovered in Europe does not exceed 10,000 per year, a few individuals are known to have survived for longer than could be expected if the early mortality were maintained. R. Perry (1953) gives records of this kind (Redwing—*Turdus musicus*, 17+ years; goldfinch—*Carduelis carduelis*, 16+ years; meadow pipit—*Anthus pratensis*, 13 years) all of them in species which have mean annual survivals of the order of 50 per cent (Lack, 1950). A ringed starling (*Sturnus vulgaris*) has been retaken after 18 years. The probability of such records being obtained as a result of chance, bearing in mind how few birds are ringed, is very low indeed. An almost exactly similar situation has been observed in the human population of the Punjab, where, in spite of a very heavy early and adult mortality, very old individuals are not uncommon, and those who survive beyond middle life have an expectation of life comparable to that in Western Europe (Yacob and Swaroop, 1945).

In lizards, the wild mortality rate declines with increasing age (Sergeev, 1939): this result agrees with the ecological studies of Stebbings (Stebbings and Robinson, 1946; Stebbings, 1948) on *Sceloporus graciosus* in the wild. A very high proportion of the population was found to consist of lizards 6 to 9 years

old (30 per cent), and there were signs of a decreasing force of mortality with age. In some cases the decrease may be even steeper. In some vertebrates the enormous infant mortality would completely overshadow subsequent trends in any life-table based upon a cohort at birth: in the mackerel, for instance (Sette, 1943), survival to the 50 mm. stage is less than 0·0004 per cent.

There are a certain number of apparent instances where senescence occurs as a regular phenomenon in wild populations of animals, both vertebrate and invertebrate, quite apart from occasional records of 'old' individuals. Murie (1944), from the examination of the skulls of 608 mountain sheep (*Ovis dalli*), constructed a life-table in which the death-rate was minimal between 1½ and 5 years of age, and climbed thereafter. The main deaths in old and young sheep appear to have been due to predation by wolves. The Arctic fin whales studied by [illegible]

specimens to return from their winter quarters to the regions where they can be caught and recorded. A good many larger carnivores and herding animals probably survive occasionally into old age in the wild state, though death must as a rule occur very early in the process of declining resistance. It is evidently impossible, in population studies, to assume either a constant mortality with age or a mortality increasing with increasing age, without some prior evidence of the behaviour of similar forms.

The 'normal' or 'wild' pattern of mortality in man is, of course, an abstraction, since even man in modern urban society [illegible] wild', albeit after much [illegible] and primitive human [illegible] heir ageing behaviour those populations of animals which occasionally reach old age, and in which the force of mortality shows some decrease during middle adult life. This is the pattern one would expect in social animals, where the survival of certain experienced individuals has probably a positive survival-value for the group, although in man the adaptation has been expressed in increasing capacity for abstract thought and social organization, rather than in

increasing longevity *per se*. Although one may guess that early man occasionally reached the point at which his powers of homoeostasis began to fail through age, he must have died through environmental pressure, like Murie's sheep, very early in the process. Out of 173 palaeolithic and mesolithic individuals whose age could be determined, only 3 (all males) appeared to have been older than 50 years, and none much older (Vallois, 1937). Palaeolithic man in the Chinese deposits normally died from violence at a presenile age (Wiedenreich, 1939). In rather more civilized societies, the fall in mortality with increasing age becomes more evident: according to Lack (1943a, 1954) the curve of mortality based on the ages given in Roman funerary inscriptions (Macdonnell, 1913) is much like that for birds. Hufeland's (1798) and Silbergleit's (Vischer, 1947) figures (Fig. 7) illustrate further stages in the transition to the rectangular survival curve of modern societies in privileged countries: many other examples have been collected by Dublin and his fellow actuaries (1949).

2.6.2 INVERTEBRATES

Senescence also occurs in the wild in some invertebrates, though it is often probably of the type of the 'parental' deaths of shotten eels. Senescence in one form or another has been invoked to account for the fixity of size and life-span in some fresh-water gastropods (Sewell, 1924; Van Cleave, 1934, 1935). The figures of Fischer-Piette (1939), relating longevity inversely to growth rate in *Patella*, also suggest the operation of senescence. It very probably occurs in the long-lived sexual forms of social insects, such as termite primaries, and has been found to contribute to the mortality of worker bees (Ribbands, 1952). Among other insects, Jackson (1940) observed a factor of senescence in tsetse flies (*Glossina*) occurring only during the rainy season, when the life-span of the flies is longer. Dowdeswell, Fisher and Ford (1940) infer the possibility of a decline in the viability of butterflies (*Polyommatus icarus*) throughout imaginal life. The position in insects is considerably complicated by the existence of specialized overwintering forms. Overwintering Gerrids show changes in the muscles which appear to precede natural death—mechanical wear of the rostrum, which occurs

in old insects, is never far enough advanced to explain their decease (Guthrie, 1953). Cladocera and Amphipoda, together with other small crustaceans, tend to exhibit constant specific age in the laboratory, and may also do so in the wild state. In a natural population of *Corophium volutator* (Watkin, 1941) the mortality in females rose sharply after maturity.

[illegible]-defined specific age in [illegible]l and Miner, 1935; L[illegible]st certainly undergo senescence with significant frequency in the wild state. A population of the tube-building *Floscularia* marked in the wild with carmine underwent a linear decline, followed by a steep increase in mortality in the final survivors (Edmonson, 1945): the curve obtained in this marking experiment was not far different from those obtained in laboratory populations of rotifers.

꩜ 3 ꩜

SENESCENCE IN PROTOZOA

3·1 *Individual Cells*

Much theoretical study was devoted during the last century to the 'immortality' of protozoans, and their insusceptibility to senescence, following the concepts put forward by Weismann. It was considered that in unicellular organisms generally, and in populations of metazoan cells undergoing division without differentiation, the product of a cell's division is always a pair of daughter cells having the same age status, and destined each to lose its identity in another division. This theory makes very important assumptions about the nature of the copying processes which underlie cell division. In the majority of cases to which it was applied, the assumptions are probably correct, although there seem to have been no direct experiments designed to show whether, in a given protozoan population, the diagram of lineages shows any tendency to segregate the deaths of individual cells towards its edges, as in a metazoan genealogy.

Weismann had been impressed (1882) that in protozoa there is no death because there is no corpse. 'Natural death' of individuals (often apparently from strictly endogenous causes) does occur in protozoa, as Jennings (1945) has shown (see below); and the assumption that there *is* no unrenewable matter at cell division is not universally true; in many forms, especially those producing swarm spores, there may be a substantial corpse, at least as tangible as the rejected parental shell of the dividing radiolarian. This is less often demonstrably the case in somatic cells, and the analogy between strictly acellular organisms and tissue cells cannot now be whole-heartedly maintained: it is still generally held, however, that the outcome of a protozoan

cell division is a pair of rejuvenated and infant cells rather than a mother and a daughter of different seniority.

The indeterminacy of cell lineages has lately been attacked with some ferocity, though on grounds of political philosophy rather than experimental evidence (Lyepeschinskaya, 1950). The question legitimately arises, however, particularly in ciliates, how far the renewal of structures at mitosis is evenly distributed between the resulting cells. Child (1915) noticed that in *Stentor* one of the progeny retains the old, while the other forms a new, peristome. From experiments he concluded that this made no difference to the age status of the inheritors, both being equally 'young'. The criterion of 'youth', however, was high susceptibility to cyanide poisoning. The critical experiment of making a genealogical table to determine the order of death of the fission products over several generations on the pattern of Sonneborn's (1930) *Stenostomum* experiments does not appear to have been carried out.

True senescence, and a marked difference in age status between mother and progeny, certainly appears to occur in suctorians. Korschelt (1922) noticed this in several forms (*Acanthocystis*, *Spirochona*, *Podophrya*, etc.), while in *Tokophrya* the parent organism's life-span can be measured, and is increased by underfeeding (Rudzinska, 1952). In a far greater number of cases, there are signs that the copying process at division only produces a new structure additional to one which already exists, not two new, or one new and one manifestly renovated, structure. The theoretical interest of this process (in *Euglypha*) and its bearing on protozoan 'age' has been noticed before (Severtsov, 1934). In such cases, either the structure does not deteriorate with time, or it is maintained continuously during life, or its possession must ultimately confer a disadvantage on one or other of the division products.

Whereas in some protozoa organelles, axostyles, flagella and cilia are visibly resorbed or shed at fission, and new ones produced for each fission product, in others, especially in ciliates, maternal organelles, flagella and other structures are shared between the progeny, being taken over by one daughter cell while copies are developed in the other. Of two closely-related species of *Spirotrichonympha* infesting termites, for example, one

divides longitudinally in the normal flagellate manner, while in the other division is transverse, the anterior daughter receiving all the extranuclear organelles of the parent cell except the axostyle, while new organs are formed for the posterior daughter. The axostyle is resorbed (Cleveland, 1938). The possibility that the 'inheritance' of organelles may modify the age status of the inheritor certainly merits re-investigation.

3·2 *The 'Senescence' of Clones*

A large part of the literature included in the bibliographies of senescence deals with the presence or absence of 'ageing' in protozoan clones. Maupas (1886) appears to have been the first to draw an analogy between somatic ageing in metazoa and the behaviour of protozoan populations. He predicted that such populations would display a life-cycle including a phase analogous to metazoan senescence, and ending in the death of the population, unless nuclear reorganization by conjugation, or some similar mechanism, brought about the 'rejuvenation' of the stock. For many years a vigorous competition was conducted between proto-zoologists in seeing how many asexual generations of *Paramecium*, *Eudorina*, and similar creatures they could rear. In the course of this process much nonsense was written about 'potential immortality', but a great deal was learnt about protozoan reproduction and culture methods. It became evident that some clones deteriorate and others, including somatic cells such as fibroblasts in tissue-culture, do not. Calkins (1919) in a classical study showed that strains of *Uroleptus mobilis* kept in isolation culture without conjugation underwent senescence characterized by falling-off of growth-potential, degeneration of nuclei, and ultimate loss of micro-nucleus. These strains ultimately became extinct. Conjugation at any stage of the process, and probably also endomixis, produced an immediate reversion to normal, regardless of whether the conjugates came from old or young isolation strains. Sonneborn (1938) succeeded, by selection of strains of *Paramecium* in which endomixis was long delayed, in breeding a race which no longer exhibited any kind of nuclear reorganization. These strains invariably died after 4 or 5 months. Rizet (1953) has recently reported similar results

with an Ascomycete kept in continuous vegetative reproduction. On the other hand, Bělár (1924) maintained *Actinophrys sol* in isolation culture, without the occurrence of paedogamy, for 1244 generations over 32 months, and observed no decline in the rate of cell division. Beers (1929) kept *Didinium nasutum* for 1384 generations without conjugation or endomixis. Hartman (1921) kept *Eudorina elegans* in active asexual reproduction for 8 years. Woodruff's oldest culture of *Paramecium aurelia* persisted for over 15,000 generations but was undergoing autogamy. The conclusion must be that some clones are stable while others are not.

More light is thrown on this problem by the work of Jennings (1945) upon clones of *Paramecium bursaria*. He found that in this species the life-cycle fell into well-defined phases of growth, sexual reproduction by conjugation with other clones, and decline. The length and character of these phases differed substantially from clone to clone. In the decline phase the death of individual cells, and especially of the progeny of conjugation between old clones, becomes very common. The vitality and viability of the progeny of conjugation, even when the conjugant clones are young, varies greatly, and a very high proportion of ex-conjugants normally die. This mortality is highest among the progeny of conjugation between related clones. Of

and a few exceptionally strong clones, some of which appeared capable of unlimited asexual reproduction. It is from these strong races that the population of laboratory cultures is normally obtained.

Jennings concluded as follows: 'Death did not take origin in consequence of organisms becoming multicellular . . . it occurs on a vast scale in the Protozoa, and it results from causes which are intrinsic to the organism. Most if not all clones ultimately die if they do not undergo some form of sexual reproduction. . . . Rejuvenation through sexual reproduction is a fact . . . yet conjugation produces, in addition to rejuvenated clones, vast numbers of weak, pathological or abnormal clones whose

pre-destined fate is early death. The rejuvenating function of conjugation is distinct from, and in addition to, its function as a producer of variation by redistribution of genes. Among the clones produced (by conjugation) there are seemingly, in some species, some clones of such vigour that they may continue vegetatively for an indefinite period, without decline or death' (Jennings, 1945).

Some authors have regarded the increased proportion of weak and non-viable conjugants of old clones as the outcome of an accumulation of unfavourable mutations. Comparable effects (Banta, 1914; Banta and Wood, 1937) have been described in clones of *Daphnia*. This was long since suggested by Raffel (1932) on the basis of *Paramecium* experiments. The type of lineal 'senescence' which occurs in *Paramecium* is in some respects analogous to the processes which are familiar in inbred stocks reproducing sexually, from *Drosophila* to domestic cattle (Regan, Mead and Gregory, 1947), and described under the general title of inbreeding depression, but differs from it in that in clones the accumulation of mutations, rather than the segregation of existing genes and the loss of the advantages of heterozygy, have been held to be involved. The mortality among the progeny of autogamy in *Paramecium* is directly related to the length of time during which autogamy has been previously suppressed (Pierson, 1938). The time scale of the group 'life-cycle' is modified by a great many physical and chemical agents—on the other hand, methylcholanthrene, normally a mutagenic agent, delays the decline of *Paramecium* clones (Spenser and Melroy, 1949).

The real mechanism of clonal senescence in *Paramecium*, however, has now been brilliantly elucidated by Sonneborn and his co-workers (in press). It depends, as other workers have foreseen (Fauré-Frémiet, 1953) on the peculiar mechanism in ciliates whereby the germinal and vegetative functions of the nucleus are divided between two separate structures. When *Paramecium* divides after a sexual process, the new nucleus of each daughter cell again divides into two. One of these products, the micronucleus, which reaches the anterior end of the cell, has the normal diploid number of chromosomes, and is apparently concerned solely with conveying the genotype: it is, in

[illegible]

nucleus divides evenly in the normal manner of nuclei, the macronucleus distributes its chromosomes at random to the daughter macronucleus arising from it. Because of the enormous number of sets which it contains, every cell in the earlier divisions has a fair chance of getting its quota, but with the passage of time more and more daughters receive an unbalanced set and a reduced physiological repertoire, and a chromosome once lost cannot be restored from the micronucleus except by sexual division—conjugation or autogamy. In the later stages of clonal senescence even sexual division is affected and abnormal or non-viable products increase. Sonneborn has shown that this is not due to the accumulation of mutations, since it can be prevented by periodic autogamy, even though this does not alter the genotype: it appears to be due to injury inflicted upon the micronucleus itself through the abnormal intracellular conditions produced by the defective macronucleus. In ciliates the germ-plasm has to live in the cell where the processes of somatic maintenance are carried out, and it is therefore unusually exposed. This is probably a unique situation—it does not even apply in other ciliates—and the division of function between vegetative and germinal nuclei is confined to this group. The existence of presumed cytoplasmic mutations, although there is no evidence to relate them to metazoan senescence as such, might be far more relevant to it than studies of protozoan clones

[illegible]

which it superficially resembles; it is doubtful if analogies can properly be drawn between acellular organisms and metazoan cells, and the only relevance of the whole question of 'ageing' in protozoan clones to ageing in the metazoan body lies in the the light which it might possibly throw upon the effects of cell division in renewing expendable enzyme systems. There is no special reason, upon the present evidence, why the 'senescence' of *Paramecium* should continue to figure as extensively as it has done in treatises devoted to gerontology.

The 'senescence' of some lines of plants in vegetative propagation apparently depend on the accumulation of exogenous viruses which hamper vigour (Crocker, 1939)—other agriculturally important varieties have been propagated vegetatively for years or centuries without deterioration. The accumulation of exogenous viruses itself raises interesting questions in regard to the possible accumulation of other, endogenous, intra- or extranuclear self-propagating materials.

Not all senescence or degeneration in clones, however, can be put down to the peculiarities of protozoa or to the action of viruses. A striking example of such a degeneration has been studied at Oxford by K. G. McWhirter, to whom I am much indebted for his unpublished observations on it. This is the condition called 'June Yellows', which affects strawberry plants propagated by runners, and impairs the formation of chloroplasts. It appears simultaneously in all plantations of a clone, even when they are geographically separated, and progresses in jumps, all the plants of the same clonal (but not individual) age passing synchronously from stage to stage. Usually in the end the clone dies out. The condition cannot be transmitted to adult plants by grafting. Transmission to seedlings is ambilinear through both egg-cell and pollen. In the progeny of crosses between clones at different stages of degeneration it is matroclinous: seedlings of very degenerate 'mothers' deteriorate most rapidly. As a clone degenerates, the tendency to transmit 'yellows' to its offspring increases. The factor or factors remain latent in some clones, but 'yellows' may appear after varying intervals in some of the selfed or crossed seedlings obtained from these clones, thus showing a latency reminiscent of that of the presumed oncogenic plasmagenes. This similarity has been pointed out before (Darlington, 1948; Darlington and Mather, 1949).

The behaviour of this degeneration is like that of a mutation which is in part cytoplasmically controlled. Such conditions are characterized by a lag-phase, by simultaneous appearance in all the members of a clone, non-infectivity, passage through a series of stable phenotypic stages, and interaction with growth and reproductive hormones. In some of McWhirter's material, 'yellows' appeared to be aggravated during the flowering period, although it may occur in seedlings long before flowering.

4

THE INFLUENCE OF GENETIC CONSTITUTION ON SENESCENCE AND LONGEVITY

4·1 *Inheritance of life-span*

4·1·1 GENERAL

IT is evident in any comparison of laboratory stocks that differences of specific age are to some degree 'inherited' (Pearl and Parker, 1922; Gonzales, 1923, Gruneberg, 1951, Fig. 31), but detailed genetic knowledge of the manner of their inheritance is not plentiful. Much variation in life-span occurs between inbred lines. This variation is often related to a single heritable predisposition to die of cancer, renal disease, or some other single cause: in these cases it is often short life, not long life, which is capable of genetic selection in the homozygote. Bittner (1937) showed that in some cases it is possible to transpose the longevities of strains of mice by cross-suckling. In other cases, secondary causes, such as restricted capacity for activity in deformed stocks, affect the life-span. In a stock of mice bred by Strong (Strong, 1936; Strong and Smith, 1936) longevity increased the apparent incidence of disease by allowing animals to reach the cancer age. Two factors appear at first sight to be involved in inherited longevity—absence of genetic predisposition to specific causes of death, and a less definite quantity ('vigour') which contributes to Darwinian fitness because it is usually expressed both in fertility and in longevity. It is by no means certain that these factors are distinct. 'Vigour' itself may in fact represent either the covering-up of deleterious recessives by heterozygosis, or a state of over-dominance, in which the heterozygote is inherently more vigorous than either homozygote.

Hereditary factors in human longevity have often been sought. Pearl and Pearl (1934a, b) found, for instance, that the summed ages at death of the six immediate ancestors of centenarians and nonagenarians were significantly greater than in a control series of the relatives of individuals not selected for longevity. 86·6 per cent of long-lived (> 70) subjects had at least one long-lived parent, while 48·5 per cent of nonagenarians

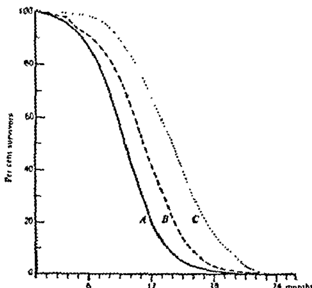


FIG. 31.—Survival curves of mice in laboratory culture—breeding females. Curve A based on 241 *dba* females, curve B on 730 Bittner albinos, curve C, on 1350 Marsh albinos (from Gruneberg, 1951).

and 53·4 per cent of centenarians had two such parents, all these figures being significantly higher than in the control series. Kallman and Sander (1948, 1949) found that in 1062 pairs of twins the mean difference in longevity between dizygotic twin individuals was twice as great as in monozygotics. These and other studies indicate that longevity is 'hereditary', but unfortunately give little light on its genetics. Beeton and Pearson (1901) studied the longevity records of Quaker families, and found that the sib-sib correlation of longevity was nearly twice the parent-offspring correlation, in those individuals who died

at 21 years of age or later, but that there was a far lower sib-sib correlation between those dying as minors. Haldane (1949) has pointed out that this is the type of correlation which would be expected where the heterozygote is fitter in the Darwinian sense

than between parent and child. In any case, the degree of parent-child correlation observed by Beeton and Pearson is only a quarter that between parental and filial statures in comparable studies.

Dublin and his colleagues (1949) have summarized most of the historic studies on the inheritance of longevity in man. They conclude that the popular idea of inheritance as a factor in longevity is probably correct, that the evidence from actuarial studies is heavily vitiated by all kinds of environmental influences, and that the order of advantage to the sons of long-lived fathers is small compared with the secular increase in life-span during recent generations. The difference in life expectation at 25 years between those with better and poorer parental longevity records is between 2 and 4 years—this compares with a gain of 6·7 years in the general expectation of life at 25 years in the U.S.A. between 1900 and 1946. 'It may be well, as has been suggested, to seek advantages in longevity by being careful in the choice of one's grandparents, but the method is not very practicable. It is simpler and more effective to adapt the environment more closely to man, (Dublin, 1949, p. 118).

It does not follow from these considerations that longer life cannot be obtained in a given population by selective breeding, and in mice this has, in fact, been done (Strong and Smith, 1936). There may well be single-gene characters where the homozygote is significantly longer-lived. 'Vigour', on the other hand, which is a correlate of both longevity and fertility, and hence of Darwinian fitness, is likely in most cases to be an expression of heterozygosis, and one would not expect to be able necessarily to produce abnormally long-lived animals by inbreeding long-lived parents.

Agricultural genetics, like natural selection, has for the most part attempted to increase lifetime production averages by

increasing early output of eggs or offspring. Greenwood (1932) found that the fertility and hatchability of hens' eggs decline with age of the parent to such an extent that attempts to improve the stock by breeding from long-lived birds were economically impracticable. Apart from the obvious difficulty

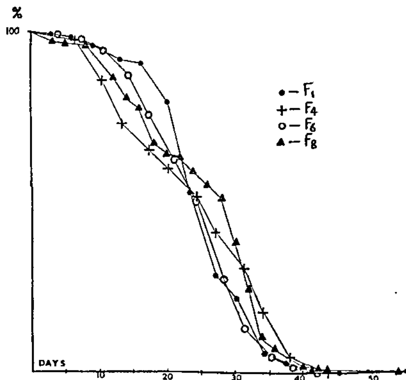


FIG. 32.—*Drosophila subobscura.* Strain K. Survival curves of flies raised in each generation from eggs laid by adults which had passed the thirtieth day of imaginal life. Compare Fig. 33.

of breeding for long life in any animal with a substantial post-reproductive period, which involves rearing all the progeny of large numbers of animals throughout life, the consequence of inbreeding *per se*, and the tendency of inbred laboratory stocks to reach a very stable equilibrium life-span (Pearl and Parker, 1922) militate against any such experiment. In Pearl's own experiments (Pearl, 1928) the long- and short-lived

Drosophila segregates were identified in the F_1 by subsidiary, anatomical characters known to be associated with the desired lines. In *Drosophila subobscura* of the structurally homozygous Küssnacht strain, which had been in culture for about three years, and had reached an equilibrium life-span considerably shorter than that of wild-caught flies, breeding for 8 generations over 1 year exclusively from eggs laid after the thirtieth day of parental life produced no significant alteration in mean imaginal longevity (Comfort, 1953) (Fig. 32).

[illegible] analysis than 'vigour', though it has been partially described in terms of response to stress (Selye, 1946). Robertson and Ray (1920) found that in a population of mice the relatively long-lived individuals formed a stable sub-group, displaying the least variation and the highest resistance to disturbing factors. In such a group the growth-rate tends to be a measure of 'general health', and rapid rather than retarded growth correlates with longevity. In other studies on groups of animals living under standardized conditions, rate of growth and length of life have been found to vary independently (Sherman and Campbell, 1935). The relation between growth-rate and vigour in a mixed population requires to be distinguished from the effect of growth retardation by dietary means in a homogeneous population, when the retarded growers live longer. As McCay (1952) points out, much early work on the relation between growth-rate and longevity was vitiated by this confusion in experimental planning.

4·1·2 PARENTAL AGE

The *age of the mother* is known in certain cases to modify the longevity of her offspring. This influence apparently include a wide range of dissimilar effects, some strictly 'genetic', and others operating at various stages in the process of embryogenesis, or, in mammals, on into lactation. Certain of these effects appear only in the F_1, while others, like the factor described by Lansing in rotifers, which leads to a decreasing life-span in successive generations of clones propagated

exclusively from old individuals, appear to be cumulative and reversible (p. 88).

The general question of maternal age effects in genetics is beyond the scope of this book. It has recently been reviewed (Miner, 1954) in a valuable symposium. In mammals the age of the mother exerts an influence on the vigour of the progeny which appears to vary greatly in direction and extent, even within a species. Sawin (in Miner, 1954) found that in one strain of rabbits, the early (< 6 months) mortality was lowest in the progeny of young mothers, and increased throughout maternal life, while in another, larger, strain it reached a minimum in the progeny of mothers 18 months old. These changes were not correlated with any differences in lactation or maternal weight. Jalavisto (1950) found evidence that in man the expectation of life decreases with increasing maternal, but not paternal, age. The percentage of abnormal offspring is greatest in litters born to young guinea pigs (Wright, 1926) and elderly women (Murphy in Miner, 1954). It is possible that the association of mongolism with high parental age is a reflection not of increasing foetal abnormality, but a decrease to the point of viability in an abnormality which, at younger maternal ages, is lethal (Penrose in Miner, 1954). In some celebrated experiments upon mouse leukaemia, McDowell and his co-workers have shown that when susceptible males are crossed with resistant females, the age of onset of leukaemia in the hybrid F_1 is significantly retarded in mice born to, or suckled by, old as compared with young mothers. At the same time, the mean longevity of mice which die of causes other than leukaemia is also greatest in the progeny and nurslings of old mothers (McDowell, Taylor and Broadfort, 1951). Strong (in Miner, 1954) has described a factor influencing the latent period of sarcoma production after injection of methylcholanthrene into mice, which appears, like Lansing's rotifer longevity factor, to be cumulative—a line derived from seventh to ninth litters in each generation had a significantly increased and increasing latent period compared with a line derived from first and second litters. Unlike Lansing's effect, this increase has not been shown to be reversible in the progeny of young members of the 'old' line. There is at present no evidence in mammals of any

cumulative disadvantage in longevity accruing to 'youngest sons of youngest daughters'. In this connection Strong has however stressed, on a number of occasions, the need for further information on the relation between longevity and cumulative parental age in human genealogies. Such information is unfortunately hard to come by, and no large-scale study has yet been published. Lansing's effect might well be sought in the parthenogenetic Cladocera. The age of the mother affects the rate of development, and probably the longevity, of young *Daphnia*. Green (1954) recently found that the size of *Daphnia* at birth determines the instar in which maturity occurs, the largest becoming mature earliest. The birth size itself depends upon maternal age, being highest (in *D. magna*) in the third brood. Since the pre-mature phase is the part of the life-cycle in which most variation occurs, the mature phase being usually of fixed length, early developers might be expected to be significantly shorter-lived than late. But R. H. Fritsch, at the Justus Liebig School in Giessen (unpublished) has compared the longevity under carefully standardized conditions of successive generations of *Daphnia* raised wholly from first, third, and sixth hatchings, and finds no significant trend in any of the orthoclones, the mean life-span in all remaining at about 30 days.

4·2 *Heterosis or Hybrid Vigour*

Abnormally long-lived animals can regularly be produced by crossing certain pure lines, not themselves unusually long-lived, [illegible]

this effect (heterosis) in increasing longevity have been recorded in mice. Gates (1926) by crossing Japanese waltzing with 'dilute brown' strains produced a generation which was still actively breeding at 2 years of age. Comparative life-tables for crosses exhibiting extreme hybrid vigour do not seem to have been published. 'Super-mice' produced by heterosis develop precociously, reach a large size, and remain in active reproduction much longer than their parents, thereby exhibiting a

combination of rapid growth with increased longevity analogous to that of the rapid-growers described by Robertson and Ray (1920). An example of the same effect in *Drosophila* is shown in Fig. 33. The greater longevity of goldfinch-canary mules compared with the parent species is apparently well known to aviarists, and such techniques of crossing are of widespread

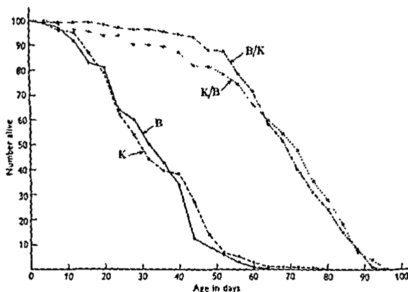


FIG. 33.—*Drosophila subobscura*—hybrid vigour and longevity. Survival curves for the inbred lines B and K, and for the reciprocal hybrids between them (sexes combined) (from Clarke and Maynard Smith, 1955).

agricultural and economic importance when applied to sheep or to plants.

The existence and magnitude of this effect should always be borne in mind in the planning of experiments on the life-span of animals drawn from closed laboratory stocks—such work can produce very seriously misleading results if unrecognized heterosis takes place. If an experiment in which the longevity of generations is compared begins with hybrid progeny, marked inbreeding depression can shorten the life-span of the succeeding generations if genetical precautions are not taken.

A fuller study of longevity in hybrids might provide useful

information on the nature of 'constitutional vigour' in relation to growth-rate. The effect is variously explained. Some of the possible complications of heterosis in relation to the criteria of vigour are indicated by the findings of Rutman (1950, 1951), who compared the rates of methionine uptake in liver slices from a fast- and a slow-growing strain of rats. The methionine replacement rate in slices derived from the fast-growing strain was almost double that in the slow, but the growth-rate of the slow strain could be made to approach that of the fast by transposing the litters during suckling, and appeared to be controlled by a milk-borne factor. Interstrain hybrids at first showed a growth pattern like that of the mother, but later followed that of the faster-growing strain.

Although by a very elegant experiment J. and S. Maynard Smith (1954) have shown that in certain cases at least heterosis appears to result from orthodox heterozygy, the number of instances in which cytoplasmic and environmental factors also appear able to evoke vigour is increasing. This is largely a reflection of the very heterogeneous character of 'vigour'. Some years ago Borisenko (1939, 1941) reported an increase in vigour in the progeny of *Drosophila* matings where the inbred parents were reared under different environmental conditions. This observation does not appear to have been repeated. The question of the induction of vigour by non-genic means has since been most actively investigated by avowed anti-Mendelians (Kurbatov, 1951; Hašek, 1953, etc.) but by no means all the positive results come from this school. As far back as 1928, Parkes observed that mice suckled by rats exhibited an extraordinary overgrowth, which results simply from excessive nutrition. Marshak (1936) found evidence of a maternal cytoplasmic factor influencing the increase of growth-rate due to heterosis in mice. The increased vigour in progeny of pure-line ova transplanted to hybrid mothers (Kurbatov, 1951) is also found in transplanted foetuses (Venge, 1953). Hašek has claimed (1953) that when parabiosis is carried out between Rhode Island and Leghorn embryos in the egg, by an ingenious technique, the pullets occasionally show even greater vigour than the progeny of R.I.R. × Leghorn crosses. Without endorsing the sweeping theoretical claims based by the Russian school upon

greater homozygosis for adverse genes, the effect should be reversed in those forms where the female is heterogametic—notably lepidoptera and birds. From the studies of Landauer and Landauer on fowls (1931) and of Rau and Rau (1914) on saturnid moths, they could find no evidence of such a reversal. Adequate life-table studies are still very scarce in these groups. In crosses, the difference in vigour between homogametic and heterogametic sexes may certainly be so great that only the homogametic reaches maturity—thus Federley (1929) found that in certain interspecific crosses in hawk moths, only the males survived pupation, though in reciprocal crosses both sexes survived. Beside these studies, that of Pearl and Miner (1936) upon *Acrobasis caryae*, which is one of the few actuarially-constructed lepidopteran life-tables which have been published, and an extensive study by Woodruffe (1951) on the survival of the moth *Hofmanophila pseudospretella* under different environmental conditions both show a significantly higher female life-span. Alpatov and Gordeenko (1932) working on *Bombyx mori*, found no difference in longevity between unmated males and females, but a significantly longer male life in mated moths. Re-examining the results of Rau and Rau (1914) they concluded that in both *Samia cecropia* and *Calosamia promethea* the mated female had a shorter life-span than the male. This difference, however, might be due at least in part to the exhaustion of reserves by more frequent egg-laying in mated females. The life-span of the female *Aglia tau* is said to be the shorter (Metchnikoff, 1907).

Rey (1936) working on the non-feeding imago of the moth *Galleria mellonella*, found that the males lived up to twice as long as the females, the difference being unaffected by humidity but exaggerated at low temperatures. He assumes this to be 'the rule for lepidoptera'.

In poultry, it seems to be established that the female is the more viable and has the longer reproductive life (Pease, 1947) and observations such as those of McIlhenny on wild ducks (1940), which indicate an increase in the proportion of males with increasing age, are probably the result of differential risks. Longer life-span in males is also found in some other birds in the wild (Lack, 1954). In cyprinodont fishes, some of which have

an atypical mechanism of sex-determination, evidence is inadequate, but Bellamy (1934) found no conspicuous sex difference in longevity in a small series. An example of longer life in the male teleost occurs in minnows (van Cleave and Markus, 1929) but this refers to a wild population. It seems altogether likely that where a sex difference in longevity is observed it arises from the sum of differences in metabolic rate and behavioural pattern—in other words, from physiological sexual dimorphism. A number of invertebrate metabolic studies support such a view (*Daphnia*, McArthur and Baillie, 1929a, b; *Drosophila*, Alpatov and Pearl, 1929), by indicating that the 'rate of living' in the male is in fact higher. The degree to which the inferior vitality of the male mammal results directly from the action of androgens has been discussed, and the whole question of male mortality reviewed at length, by Hamilton (1948). In man, the higher male mortality is present both *in utero* and in infancy. At later ages the question is, of course, complicated by social and occupational factors (Herdan, 1952). There are as yet no fully satisfactory human data upon the relative longevity of castrates, though their life-span is certainly not grossly inferior to that of normals. Many of the highest recorded ages in cats have occurred in gelt males (p. 48). The finding of Slonaker (1930) that castration produces a slight decrease in rat longevity was based on too few animals to be significant.

In some instances (*Drosophila*, Bilewicz, 1953) the life of the male is still further shortened by copulation. In others (*Latrodectes*, Shulov, 1939–40) the male dies after a determinate short life-span, whether mated or not. While the mortality of Anglican clergy in England during the 1930's was only 69 per cent of [illegible] and that of other Protestant clergy

mating improves the condition and longevity of the male (Agduhr, 1939; Agduhr and Barron, 1938). This might tend to support the view that the virtues of 'continence' in man, vis-à-vis longevity, have been over-praised by interested parties. After citing the opinion given by the Dutch physician Boerhave

(1668–1738), who 'recommended an old Burgomaster of Amsterdam to lie between two young girls, assuring him that he would thus recover strength and spirits', Hufeland (1798) remarks 'We cannot refuse our approval to the method.' It would seem by tradition to be applicable only to the male.

4·4 *Progeria*

Although the rate of senile deterioration varies between individuals, the specific age of genetically homogeneous animal lines is very stable; even in human populations the range of apparent variation is not very great, and the few descriptions of racially-distributed 'premature senility', as in Eskimos (Brown, Sinclair, Cronk and Clark, 1948) are not actuarially supported, though such variation, genetic or environmental, may occur.

Sporadic cases of syndromes having some of the general characters of premature old age occasionally occur in man. It is not clear how far any of these syndromes can be regarded as genuine accelerations of the timing mechanisms which determines senescence. They are apparently pleiotropic genetic defects, occurring commonly in sibs, and are most conveniently mentioned here. They have been regarded as pluriglandular endocrine disturbances, but they affect many ectodermal structures and have the rather generalized character more typical of an inborn error of metabolism—possibly the deficiency of an enzyme system.

Infantile progeria (Hutchinson-Gilford syndrome) (Thomson and Forfar, 1950; Manschot, 1940, 1950) occurs in childhood. After an apparently normal infancy, the child begins to show retarded growth, with dwarfism and progressively increasing physical abnormality. The appearance becomes senile, the skin atrophic, and there is hypertension with extensive atheroma and calcification. Death usually occurs from coronary disease before the thirtieth year. The mental development of these children may be retarded, but is more typically precocious. Cataract may occur. The endocrine appearances at necropsy are inconstant, but pituitary eosinophiles are reported to be reduced (Manschot, 1940).

Adult progeria (Werner's syndrome) was first described by Werner (1904) in four sibs. It bears some resemblance to a delayed infantile progeria, occurring after growth has been wholly or partially completed. The subjects are short and of unusual appearance. The symptoms begin in the third or fourth decade, with the development of baldness, greying, skin changes, cataract, calcification of vessels and occasionally of tissues, osteoporosis, hypogonadism, and a tendency to diabetes (Thann-

Thannhauser (1945) and by Thomson and Forfar (1950).

laboratory animals. In infant progeria, pituitary growth-hormone deficiency appears to play some part, though the condition differs markedly from straightforward dwarfism. The deficiency of oxyphil cells in some reported cases bears a resemblance to that which follows castration (Wolfe, 1941, 1943).

Sudden 'senescence' in adults, a great standby of the nineteenth-century dramatist, is an uncommon endocrine, or possibly hypothalamic, reaction to severe emotional shock or accident, which, although not genetic, can conveniently be considered here because of its superficial affinity with progeria. In the interest of literary effect, the preliminary phase of sudden baldness is usually not stressed. The hair may fall out within twenty-four hours, to be replaced when it grows again after an interval, by white or structurally defective hair—impotence, depression and cachexia are described as concomitants. The condition is recoverable, and appears to have more connection with Simmonds' disease than with senescence. A case was reported by Greene and Paterson (1943) in a railwayman who fell from a locomotive and suffered head injury and severe shock. A few cases are alleged to have followed intense fear, as in battle. The pituitary may well be the endocrine chiefly responsible.

4·5 *Choice of Material for Experimental Study of Age Effects*

Research on the senescence of man and most large mammals necessarily involves work on genetically diverse populations. Where closed laboratory stocks are used, or the subject is a 'genetical' domestic animal such as the mouse or *Drosophila*, genetic precautions are essential in ageing experiments, especially if comparisons are to be made between the life-spans of different groups or different generations. The size of the effect which can be produced in such stocks by heterosis has already been mentioned. The presence or absence of uniformity in the experimental population is also particularly important in research involving life-tables, since in many inbred lines the form of the life-table depends entirely on one cause of death which is not typical of the species, or even the phylum.

In non-genetical experiments (nutrition, biochemistry, growth-rate and so on) the choice lies between *inbred, hybrid* and *random-bred* material. *Inbred* lines commonly have a life-span which is rather low for the species, and this may be advantageous. Their vigour is often low, though inbreeding depression is more evident in some species than others. Inbred lines are often chosen by non-genetical workers for bioassay, in the belief that they have the advantage of uniformity. This, however, is not so. Gruneberg (1954) has stressed two important characters of such lines: they cannot be relied upon to remain constant in their heritable properties with the passage of time, and may diverge rapidly when split into separate colonies; and they do not constitute phenotypically uniform material, but may, on the contrary, be strikingly more variable than F_1 hybrids between strains, and even than random-bred material (McLaren and Michie, 1954).

Hybrid material, bred in each generation by crossing inbred lines, suitably chosen, has a number of important advantages for general work upon ageing. In such crosses the life-span approaches the maximum for the species under the experimental conditions. Vigour is high, so that 'background' losses due to temperature change, infection, operative mortality and accident is much reduced, and variation between individuals is minimal. This uniformity is itself probably a reflection of

vigour, in the form of better homoeostasis (Robertson and Reeve, 1952). Hybrids can, like inbreds, be employed for transplantation experiments. Like inbreds, too, they may all die of a single cause, and will do so as a rule with greater unanimity in regard to age.

Random-mated material, when mating is genuinely random, and not occurring within an already highly-inbred colony or between such colonies, produces animals, the strongest of which exhibit a vigour and life-span approaching that of hybrids, more variable than hybrids, unsuitable for transplantation experiments, showing a variety of causes of death more closely resembling that in human populations, and, in general, resembling such populations more closely than hybrid or inbred lines.

The choice of inbred, hybrid, or random-bred material, when it is not dictated by the fact that no pure lines are available, will depend upon which of these attributes are most useful. The type of material must, however, be correctly stated, since it greatly affects the interpretation of results. Probably the most valuable approach to the comparative study of ageing, though not always a practicable one, would be a scheme of research carried out in parallel upon all three types of strain, in an animal which is already genetically familiar.

5

GROWTH AND SENESCENCE

5·1 *'Rate of Living'*

THE idea of the life-span as a fixed quantity is an old one. In a great many organisms it has long been recognized that the contrast, perhaps originally moralistic, between a long life and a high 'rate of living' had valid biological applications. The phrase 'rate of living' we owe to Pearl, and it conveys the concept very satisfactorily without making too many assumptions. In many organisms the life-span, like the rate of development, is a function of the temperature over a considerable range. In such forms it appears that a fixed quantity of *something*, which, for want of a better term, we have called 'programme', must run out and be succeeded by senescence. The organism must pass through a fixed sequence of operations, metabolic or developmental, the rate of its passage determining the observed life-span.

The period in which the kinetics of metabolism were being discovered expressed this 'programme' in directly chemical terms. Life had an observable temperature-coefficient. Growth, in the classical conception of Robertson (1923), followed the same course as a monomolecular autocatalytic reaction. Loeb (1908) attempted to answer by the determination of temperature coefficients a fundamental question about the 'rate of living' in relation to ageing—what is the nature of the 'programme' which has to be fulfilled before senescence begins? Is it a programme of differentiation, or growth, or maintenance metabolism, or of all three? Loeb's experiments showed that the temperature coefficient of the rate of 'ageing' in echinoderm ova differed greatly from that of their respiration. Later work has shown the relationship between development and tempera-

ture to be too complex for simple estimation of coefficients. Morphogenesis depends upon a large number of simultaneous and occasionally contrary processes. We should almost certainly now be inclined to interpret the programme fulfilled by an animal during its life-cycle in terms drawn from experimental morphology and from the study of control systems, rather than directly from physical chemistry.

The postulation that senescence always accompanies, or follows, the cessation of growth, which certainly appears to fit many of the observed facts, we owe originally to the work of Minot (1908). It is, in fact, no more than a postulation, since, as we have seen, there may be organisms in which senescence occurs hand-in-hand with growth, and there are certainly organisms, such as terrapins, which have a virtual maximum size but are not known to exhibit senescence. Senescence in man, judged by the life-table, commences while active growth is in progress: Minot himself considered that the rate of senescence was actually greatest when growth rate was at its maximum. If the relationship between senescence and growth-cessation is real, it might mean (1) that that which 'causes' the cessation of growth also causes senescence—implying that growth-cessation results from an active and inhibitory principle, (2) that that which no longer grows, senesces, (3) that growth-cessation and senescence are parallel phenomena, both arising from the process of differentiation.

The dissociability of growth from development was first shown by Gudernatsch's researches upon the action of thyroid in the developing tadpole (1912). Metabolism, measured by respiration, is dissociable from both. 'The fundamental mechanisms are not separable only in thought: on the contrary, they can be dissociated experimentally or thrown out of gear with one another' (Needham). The fundamental problem in relation to the 'rate of living' lies, therefore, in determining which of these processes, and in what proportions, make up the essential sequence of operations through which the organism must pass before senescence makes its appearance. In its crudest form the question is: given that these processes, though dissociable, are normally interdependent, does this organism undergo senescence (1) when it reaches a particular stage of cellular

differentiation, (2) when it has exhausted a particular store of 'growth energy', whatever the nature of such a store, or (3) when it has carried out a certain stint of metabolism—a life-span measurable in calories or in litres of oxygen consumed? It is immediately evident that the programme in real organisms is complex, that since senescence is a diverse process the pacemaker differs in different forms. In some cases, when (1) above has been satisfied, the further life-span of the *differentiated* cells may depend upon their metabolism, as in (3). All concepts based on 'wear and tear' in neurones or other cells postulate a similar sequence: loss of regenerative power followed by mechanical or chemical exhaustion. In the rotifer the normal sequence of differentiation produces an organism which is almost incapable of cellular repair, and quite incapable of nuclear regeneration. The life-span of the adult, once this point in the programme has been reached, is inversely proportional to temperature and metabolic rate over a certain range. How this effect operates we do not know. The encysted adult, although unable to survive in the complete absence of oxygen (Rahm, 1923) may pass years in diapause. The life-span of many larvae can be enormously prolonged by underfeeding or accelerated by heating: once metamorphosis has taken place the programme is resumed but still responds to changes in temperature by a change in pace. The longest-lived imagines, termite queens, do in fact increase in size after eclosion (Harvey, 1934). In mammals it has been postulated that, since the metabolic rate is held steady by various homoeostatic devices, the essential ingredients of the programme leading to senescence are growth and differentiation; that growth ceases as a result of some process or processes of differentiation, and that the absence of growth is a proximate cause of senescence.

We have already suggested that this is not wholly in accordance with the evidence. The observational test, that no vertebrate which continues to grow undergoes 'morphogenetic' senescence, and that all vertebrates which cease to grow are subject to it, does not appear to be satisfied, while the experimental test, the demonstration that the life-span of an adult vertebrate can be prolonged by keeping it artificially in continued growth, beginning after normal size and development have been at-

tained, has not been carried out, although there is some evidence that it may be experimentally feasible. We cannot yet identify any single process which, by its failure, produces the senile decline of homoeostasis in mammals. It is however possible to treat the developmental sequence leading to senescence, in its relation to growth and to differentiation, as an 'integrating system', of the type employed in various calculating and timing devices.

The most familiar example of such a system, functioning as a calculating device, is the taxi-meter. This machine records time when the taxi is stationary, and distance, or time and distance, when it is moving. The real taxi-meter does so upon an 'open-ended' scale, the amount of the fare which can be rung up on the the dial being theoretically unlimited, since the dials after reaching £99 19*s*. 11½*d*. return to zero. For the purpose of our argument, the biological taxi-meter has been adapted by an anarchist to produce an undesirable result when a particular fare is reached—say £10; or, more correctly, an *increasing prob-*

the taxi is stationary, and half a crown per mile plus one shilling per minute so long as it is moving. In this case, if the journey never begins, the impairment will take place eventually, though not for a very long time. For an extended biological analogy it is probably better to take the case in which the conditions of the

tage are, first, that the fare
he taxi shall have travelled
arting point.

The question we have to ask is this: does mammalian senescence effectively resemble such an integrating system, in which differentiation is the higher-scoring and the essential component, but in which retardation leading to continuance of growth directly or indirectly delays the point at which senescence appears; or does cessation of growth *itself*, whether it arises from some active mechanism of size limitation or through the attainment of an equilibrium state, directly cause the senile deterioration? The crude application of the calculating-machine or the time-fuse analogy has many objections, the chief of them

being that the senile decline in resistance in mammals is not a sudden process, as it is in the rotifer, but a smooth rise in the force of mortality beginning at an early stage. Mechanical timing devices produce as a rule a single event after a fixed programme, not an increasing probability throughout the programme, though this objection does not hold good for analogue computing systems: it is relatively simple to devise an electronic taximeter-bomb in which the *probability* of an explosion increases with the increase of time and distance, or a system in which the steering of the taxi becomes increasingly impaired as the 'programme' continues. A far more serious objection is that in ordinary taxi-meters time and distance are not normally interlocked, as growth and differentiation, though experimentally separable, are interlocked in the developing animal. It has been suggested that the two processes are in some degree mutually exclusive (Bertalanffy, 1933, 1941)—a conception which goes back to Minot. It seems probable that in most organisms it is the component of differentiation, not that of mere growth, which is responsible for senescence.

Analogies, in any case, are mostly of use as teaching-illustrations. In the final analysis, senescence, even if it never reaches the ideal state of being expressed as a sequence of chemical reactions and equilibria, must presumably be reducible to a series of definite processes—such-and-such a mechanism leads to the loss of dividing-power in such-and-such cells, which then have a life-span limited by the non-renewability of their enzymes to so many chemical operations, after which they deteriorate with the following consequences. We are nowhere near such a picture of any one senile or developmental process in any organism, let alone of mammalian senescence or morphogenesis in general. A certain amount of experimental evidence has, however, accumulated—enough to indicate the directions in which further research might profitably be directed.

5·2 *Experimental Alteration of the Growth Rate*

5·2·1 INVERTEBRATES

In many invertebrates, the specific age is easily altered, either in response to temperature changes, to which it bears a simple relation, or by retardation of growth through the restriction of food. The total longevity of insects can be increased either by underfeeding the larvae, or by keeping any or all of the stages, from egg to imago, at low temperatures. The same applies to ticks—starvation will increase the life-span of some species from a few weeks to 2 years (Bishopp and Smith, 1938). Northrop (Northrop, 1917; Loeb and Northrop, 1917) kept *Drosophila* larvae for varying periods on a yeastless medium to delay growth and induce stunting: by this means the total life-span from hatching to death was increased. There is disagreement whether delayed growth of larvae leads to an increase in the life-span from eclosion. Northrop found no such increase in imagines reared from retarded larvae. Intermittent starvation of the imago of *Drosophila* shortens its life; retardation of the larvae of *Lymantria* also fails to increase the life-span of the imago, which cannot feed (Kopeć, 1924, 1928). Alpatov and Pearl (Alpatov and Pearl, 1929; Alpatov, 1930) found a slight increase in imaginal life-span in *Drosophila* when the larvae were retarded by development at 18°. This effect was less evident in males, and appeared to be reversed in some experiments: where the imagines were kept at 25–28° larvae reared at 28° gave longer-lived flies than those reared at 18°. The statistical significance of the differences was in any case small.

The life-span and final size of *Daphnia* (McArthur and Baillie, 1926) and *Moina* (Ingle, 1933; Terao, 1932 etc.) vary inversely with the temperature over a considerable range. Like *Drosophila*, *Daphnia* can be markedly retarded either by cooling or by underfeeding. A detailed study on the effect of retardation upon specific age and growth in *Daphnia* was carried out by Ingle, Wood and Banta (1937). By diluting the medium, it was shown that starvation of *Daphnia* for varying numbers of instars resulted in an increase of life-span approximately equal

to the period of starvation, but that individuals starved only until the 11th or 17th instar lived longer than individuals starved throughout life. This prolongation of life was achieved

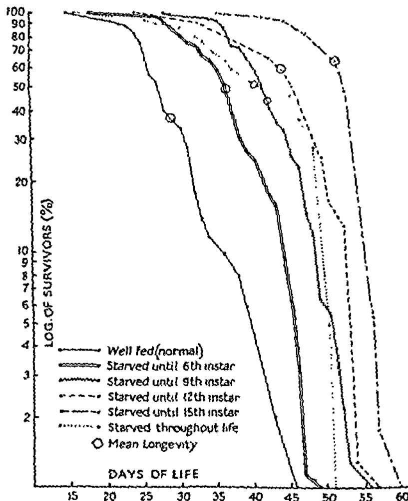


FIG. 37.—Effect of restricted food upon the longevity of *Daphnia longispina* (from Ingle, Wood and Banta, 1937).

by lengthening the duration of each retarded instar, the total number of instars remaining constant. In this species (*D. longispina*) the specific age appeared to lie between the 19th and

22nd instars, without reference to the chronological age which these may represent. (Figs. 37, 38, 39.) In *D. magna*, Anderson and Jenkins (1912) found a mean life-span of 960 hours or 17 instars—the number of pre-adult instars varied from 4 to 6 and

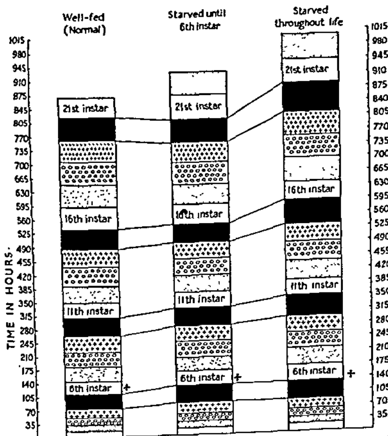


FIG. 38.—Effect of restricted food upon the duration of instars in *Daphnia longispina* (from Ingle *et al.*, 1937).

the differences in longevity between individuals represented differences in the length of the pre-adult period. (See also Dunham, 1938.) The finding of Fritsch (1953) that the pantothenic acid content of the medium is a major factor in

determining the life-span of *Daphnia* complicates the interpretation of some of these studies of dietary retardation, however.

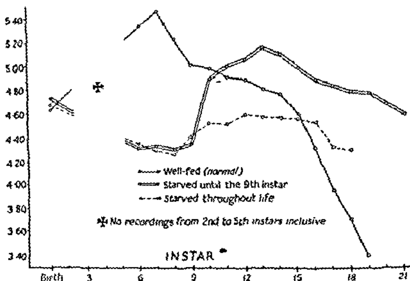


FIG. 39.—*Effect of restricted food upon the rate of senile change in the heart rate of Daphnia longispina* (from Ingle *et al.*, 1937).

5·2·2 INSECT METAMORPHOSIS AND SENESCENCE

A great many insects are capable of very long pre-imaginal life, the duration of which is largely determined by food supply. The 'rate of living', as a simple quantity treated apart from morphogenetic processes, does not give an entirely satisfactory picture of insect development. We might possibly make an experimental approach to the study of insect senescence on the following lines. Senescence, of course, occurs in the ordinary course of events only in the imago. The larval or nymphal stages must be regarded as a system which is self-maintaining but which tends towards ultimate metamorphosis. They are analogous to the young growing period of non-metabolous metazoa. The question arises how long, if metamorphosis could be indefinitely prevented, the metathetelic larva would remain self-maintaining as an equilibrium system. It might presumably do so indefinitely, or it might ultimately undergo a specialized

type of senescence due to the suppression of development or to imbalance between continued, divergent growth processes; or it might nevertheless undergo senescence from the same cause, whatever that cause may be, which limits the life of the imago.

To ask whether a larva or a nymph would senesce if it did not metamorphose is not entirely idle speculation. The data which we have on the developmental physiology of *Rhodnius*, chiefly from the work of Wigglesworth, make it possible to contemplate interfering with the development of nymphs. The pre-imaginal phase of *Rhodnius*, during which growth takes place, is maintained by the so-called juvenile hormone. 'During larval life, imaginal differentiation is suppressed because in the presence of the juvenile hormone secreted by the corpus allatum the intracellular system which leads to the production of larval structures takes precedence over the system which leads to the formation of adult structures' (Wigglesworth, 1953b). The influence of temperature on larval development appears to act through this system, high temperatures or low O_2 tensions depressing the juvenile hormone and producing prothetely, low temperatures enhancing its effect and producing metathetely. This system lends itself particularly well to analysis in terms of control-mechanisms. The tendency of the cellular system in its 'free-running' state appears to be towards the imaginal form. Moulting hormone from a fifth-stage larva will cause a first-stage larva of *Rhodnius* to metamorphose (Wigglesworth, 1934). Second-instar moth larvae will metamorphose to minute pupae and adults if the corpora allata are removed (Bounhiol, 1938) and isolated fragments from the integument of newly-hatched moth larvae tend to pupate (Piepho, 1938). The function of the juvenile hormone appears to be to moderate or prevent this free-running tendency, though as a standing bias, not as a negative feedback. The point to which the free-running system tends, moreover, is an unstable one, ending in eventual senescence. In the fifth stage *Rhodnius* nymph the thoracic gland undergoes very rapid disintegration as soon as metamorphosis takes place, and the possibility of moulting and cuticular renewal is thereby lost, from lack of evocator, although the power of the dermal cells to respond to injected moulting hormone remains (Wigglesworth, 1953a). Long-term change

in this system causes the bias to be overcome at the correct moment. The homoeostasis achieved by the juvenile hormone is not absolute, otherwise metamorphosis would never take place; the metamorphosis-producing hormone ultimately carries the day. But occasional nymphs of *Rhodnius* devoid of the thoracic gland cannot metamorphose, and appear to live for long periods without senescence. This mechanism offers an opportunity for the dissection of just such a system of partial homoeostasis, directed to act as a delay-mechanism, as appears to underlie so many life-cycles which end in senescence. Work on insect senescence is in many respects unpromising as a source of principles which can be extended to the biology of vertebrate old age; such research is frequently confined to the very special circumstances which exist in the imago—in other words, to a system which is already in a time-limited equilibrium. For measures of interference with the growing organism, however, and attempts to stabilize the system in its earlier stages, insect material may prove the most manageable. Any example of indefinite stabilisation at an immature stage, in any organism, would be of great biological interest. The degree of drift towards the unstable state probably varies throughout development in different insects—Bodenstein has shown (1943a, b) that in *Drosophila* early salivary glands implanted in late larvae are not *immediately capable of metamorphosis*: '*Whether the organ* discs respond with growth or differentiation depends on a definite relationship between hormone concentration and organ responsiveness' (Bodenstein, 1943b).

5·2·3 VERTEBRATES

The possibility of producing a long-lasting but recoverable delay in mammalian growth and development by underfeeding first arose from the studies of Osborne and Mendel, (*1915*, 1916). The work of McCay on rats, which extended the results obtained by underfeeding upon arthropod growth directly to mammals, is well known, but still very remarkable. It also still represents the only successful assault which has ever been made *on the problem of mammalian specific age, which is itself the* key problem of medical gerontology; and the rather exceptional growth-pattern of rats in no way diminishes its interest. The

experiments, first described in 1934 (McCay and Crowell, 1934) extended over years, and are fully reviewed in retrospect by McCay (1952). Groups of rats were reared on a diet sufficient in all other constituents but deficient in calories, and their growth thereby retarded. After periods of retardation up to 1000 days, the caloric intake was raised to permit growth. The animals then grew rapidly to adult size, even though the longest-retarded group had already exceeded the normal life

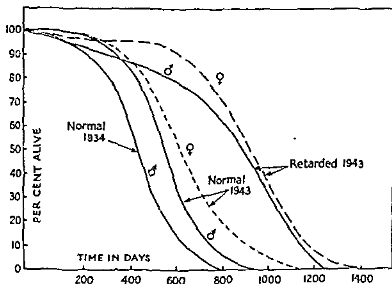


FIG. 40.—Survival curves of normal and retarded male and female rats, showing the effect of dietary restriction (from McCay, Sperling and Barnes, 1943).

span for the strain, and continued to live to approximately twice the maximum age reached by unretarded controls (Fig. 40.) This long survival was accompanied by a decreased incidence of many chronic diseases, which appeared to represent a true diminution in senile liability to death from random causes. The chief specific diminution was in death-rate from pulmonary diseases and from tumours. 'In general, the retarded rat remains active and appears young whatever its chronological age. It is very alert. It tends to go blind in the second

and third year of life. Its pulse rate of 340 beats per minute is about 100 below normal' (McCay, 1952). The basal metabolic rate of rats so retarded lay between that of normal young and normal old animals (Horst *et al.*, 1934). In rats retarded for 850 days, heat production per unit surface area was lower, but heat production per unit weight higher, than in normal controls (Will and McCay, 1943). The aorta and kidneys of retarded rats showed in general a higher level of calcification than those of controls (Hummel and Barnes, 1938) perhaps on account of the relatively higher mineral concentrations in the restricted diet (Barnes, 1942). A further series of experiments in the dietary restriction of animals which had already reached maturity was unfortunately complicated by the introduction of many groups of variables (exercise, casein intake, liver supplements, etc.)—in these experiments, underfeeding produced a significant increase in life-span compared with fully-fed controls, but the difference was far less conspicuous than in the retardation of young growing rats, and the factors which were most important in determining life-span were those which determined the degree of body fatness (McCay, Maynard, Sperling and Osgood, 1941: Silberberg and Silberberg, 1954). This difference was largely accounted for by the higher incidence of renal disease on a high protein diet and in obese animals (Saxton and Kimball, 1941); in contrast to the findings in animals retarded while young, the incidence of chronic pneumonitis and of tumours was not reduced by underfeeding in mature animals (McCay, Sperling and Barnes, 1943; Saxon, 1945). A 33 per cent restriction of calories, other elements in the diet being unaltered, produces a significant prolongation of life in male C3H mice (King and Visscher 1950).

The results of these experiments indicate that at least some mammals are capable while immature of undergoing prolonged suspension of growth without any acceleration of senescence. The suspension is not complete, since deaths occur unless some increase in weight is allowed. The most important inference to be drawn from the work would appear to be that senescence itself is the direct consequence not so much of growth-cessation as that of the attainment of a developmental stage, the timing of which is partially, but not wholly, linked to the growth-rate

—there being no evidence that starved rats remain 'young' indefinitely. By 1150 days, moreover, only about half the retarded individuals were capable of resuming growth (McCay, Sperling and Barnes, 1943). There is some evidence from later work that prolongation of the life-span, though in a smaller degree, can be produced by intermittent dietary restriction without any evident effect on the growth-rate (Carlson and Hoelzel, 1946). Moreover most of the changes which ultimately fix the specific age appear to have occurred at the time of maturity, since the increase in longevity obtained by underfeeding, adult [illegible]

lowers the gonadotrophic activity of the pituitary: this was clearly shown by the transplantation studies of Mason and Wolfe (1930) on female rats, and again in male rats by Moore and Samuels (1931). In rats, reduction of the protein content of the diet below 7 per cent produces anoestrus from gonadotrophin deficiency (Guilbert and Goss, 1932). In the 'pseudohypophysectomy' of malnutrition, pituitary growth hormone will re-initiate growth of the skeleton and decrease the rate of weight loss even without increase of food intake (Mulinos and Pomerantz, 1941). The subject was reviewed by Samuels (1946). The relationship between this 'pseudohypophysectomy' and McCay's results is not yet clear, but the effects of restricted food intake on the pituitary probably play a major part in the alteration of apparent specific age.

In C3H mice, Carr, King and Visscher (1949) produced anoestrus by reducing the standard calorie intake by half: at 14 months of age, single cycles were readily induced by administering dextrose, though the dose necessary to bring this about varied from 0·15 to 1·0 gm. When the mice were permitted at the age of 21 months to feed at will, and mated, all became pregnant, and 10 out of an initial total of 17 were alive and sexually active at the age of 23 months.

We have no comparable observations in man. Malnutrition can produce gross retardation of puberty (as can disease or 'indirect' malnutrition—the effects of bilharzia are particularly striking) but such malnutrition is always total, and shortens life.

In McCay's experiments the dietary restriction was confined to reduction of calories. The undernourished majority in the world at the present time derive no benefit in longevity from their circumstances. But it is not impossible, as Edmonds suggested in 1832, and as Sinclair (1955) and McCance and Widdowson (1955) have repeated, that adult life may be shortened by the pursuit of excessively rapid growth during childhood. Human puberty can be accelerated by overfeeding (Bruch 1941), and there is already evidence that while the maximum mean height of Englishmen has not increased during the last century, it is now reached no less than five years earlier (Morant 1950), and the loss of height with increasing age shows a parallel advance.

In 1948, Evans, Simpson and Li confirmed with pure growth hormone Wiesner's (1932) original finding that rats could be kept in continuous growth throughout life by injections of pituitary growth hormone. Wiesner had reported some improvement in the condition of old male rats under the influence of growth hormone. The experiment of Evans, Simpson and Li was not designed to study the effect of growth on longevity, and they found that continued growth from hormone administration in rats itself leads to death from an increased incidence of tumours. The 12 animals in the original experiment of Evans, Simpson and Li were killed at 647 days for histological purposes. With small doses of the purified hormone, 'drug-resistance' to the growth-promoting and nitrogen-retaining effects develops (Whitney, Bennett, Li and Evans, 1948). In dogs, and cats, continued administration of growth hormone after growth *cessation* produces not growth but diabetes, while in others (man) epiphyseal fusion prevents continued body growth after sexual maturity. Although the response of rats both to retardation and to growth hormone is apparently atypical, and certainly differs from that which might be expected in man, the possibility exists of comparing in a mammal the effects on rate of senescence of (1) retarded growth to the full specific size, (2) of accelerated growth up to, and beyond, the specific size, and (3) of growth beyond the specific size, but beginning in old age. Apart from the complication of tumour production, the general endocrine effects of growth hormone are likely to be

too extensive for simple life-table experiments, but its use as a [illegible]

1952) found that massive administration of growth hormone (2 mg./day) to mice evoked tumours in only one of the tested strains. It appears, moreover, that growth hormone alone fails to induce tumours in hypophysectomized animals (Asling *et al.*, 1952a, b). The resistance which develops to the heterologous (ox) hormone used in such experiments may perhaps be surmountable. The idea underlying this kind of investigation was already present in the work of Robertson (Robertson and Ray, 1919; Robertson, 1923) at a time when endocrinology was insufficiently advanced to enable it to be realized. The results they obtained in retarding growth with 'tethelin' were almost certainly non-specific. Work upon growth hormone in mammals whose epiphyses do not unite would appear to be one of the critical experiments in finding out how far growth and development are an integrating system tending to senescence at a fixed point, and how far mere growth, induced by one of many anabolism-stimulating factors, is capable of reversing or preventing senile change.

Attempts to *accelerate* mammalian senescence have been surprisingly unsuccessful. While laboratory animals can be prematurely killed by a number of drugs or deficiencies, these do not in general affect the process of senescence. Experimental efforts to accelerate ageing in rats with dinitrophenol (Tainter, 1936, 1938) and thyroid (Robertson *et al.* 1933) or retard it with thiouracil (Hartzell, 1945) have been uniformly unsuccessful in bringing about any change in the specific age. Petrova (1946) obtained evidence that induced neurosis at least shortens the life, if it does not affect the specific age, in dogs: it is significant that in man the most effective means of reducing the apparent rate of senile change, *ceteris paribus*, are psychological, social and occupational.

5·3 *Growth-cessation and Mammalian Senescence*

Mammals in captivity under 'optimal' conditions exhibit both specific size and specific age, and these vary widely

between related species, and between genetic races of the same species. The mechanism which determines specific size has long been believed by some workers to intervene more actively in mammalian development and to be more selective in its action on tissues, than the mechanism which leads to the more gradual decline of growth in some reptiles and fish. In these forms, according to this view, the die-away curve of growth, which is generally exponential in relation to body weight, suggests a far more general process of size-limitation affecting all the tissues approximately equally, and reaching the virtual limiting size without much alteration in the general physiology of the animal. 'It is the rule in fishes and other cold-blooded vertebrates that growth is asymptotic and size indeterminate, while in warm-blooded animals, growth comes, sooner or later, to an end. But the characteristic form is established earlier in the former case, and changes less, save for . . . minor fluctuations. In the higher animals, such as ourselves, the whole course of life is attended by constant alteration and modification of form' (D'Arcy Thompson, 1942). The form of the mammalian, and especially the human, cycle both of growth and of senescence has frequently been interpreted as an active process of negative feedback, which operates unequally, which may contribute to the relatively sharp arrest of growth at the level represented by the specific size, but which results in a 'morphogenetic' senescence depending in turn upon a rather limited number of key physiological changes.

With the hypothetical relationship between growth-cessation and senescence in mind, a number of attempts have been made in the past to interpret senile changes in terms of endogenous 'growth inhibitors', whether these are regarded as substances or as physico-chemical conditions (Baker and Carrel, 1926; Carrel and Ebeling, 1921; Simms and Stillman, 1936). The case for such an inhibiting system was stated by Bidder (1932) in the passage already quoted (p. 12). The nature of influences determining mammalian organ size is virtually unknown. Some of these appear to be extra-cellular and inhibitory. In cultures, e.g. of diatoms, growth may be arrested by the accumulation of a metabolite (Denffer, 1948). The most primitive types of morphogenesis, such as that found in hydroids, depend on the

acquisition by certain zooids of inhibitory powers over the development of others (Summers, 1938), although the inhibited cells retain the potentiality of growth. It is also known that some 'old' tissue cells are capable of indefinite growth in cultivation.

The suggestions implicit in this type of reasoning are tempting, but there are evidential grounds for caution in postulating a simple, 'toxic' senescence due to the existence of a growth-inhibiting senile principle. Such a principle is not readily demonstrated. Bidder once rashly located it in the pineal gland. Kotsovsky (1931) attempted successfully to retard the growth of tadpoles by feeding senile heart muscle—an improbable tissue for such a purpose—and Grimm (1949) obtained similar results with senile plasma. Picado (1930) enhanced the growth of young rats by transfusions of adult plasma. More serious data, however, exist.

The best experimental evidence concerning growth-limitation is probably that obtained from studies of mammalian liver. Although mitotic figures and binucleate cells decrease in mammalian liver throughout life, regeneration after hepatectomy occurs in senile rats, apparently at a rate not much lower, so far as replacement of cell number of concerned, than in young adults, though much less than in growing animals (Bucher and Glinos, 1950). As Minot pointed out (1908) the adult differs more from the infant than the old from the adult. The time lag between hepatectomy and maximum mitotic count increases with age (Marshak and Byron, 1945), thereby paralleling the difference between the behaviour of tissues from young immature and young adult donors in tissue culture (Hoffman, Goldschmidt and Doljanski, 1937), and confirming the universal finding of increased growth-inertia, rather than decreased growth capacity, as the most conspicuous character of cellular explants with increasing donor age (Cohn and Murray, 1925; Suzuki, 1926; Medawar, 1940). In regenerating rat liver at all ages, however, the lag reverts to the value characteristic of young animals (Glinos and Bartlett, 1951). In young, actively growing rats the restoration of liver mass after hepatectomy shows a considerable rebound phenomenon, reaching 145 per cent of the original weight in 7 days (Norris, Blanchard and

Polovny, 1942). All the general characters of tissue behaviour during the attainment of specific size appear to be exemplified in liver. These include (1) negative specific acceleration of growth, (2) retention of growth capacity after the limiting size has been attained, as demonstrated either by explants, or, in this case, following partial removal of the organ, (3) increased growth inertia with increasing age and (4) 'post-inhibition growth rebound'. Medawar (1942) stresses the surprisingly wide distribution of this last effect, which is shown by tissue cultures (Spear, 1928) and *Amblystoma* larvae (Buchanan, 1938) retarded by cooling, and in rats or mice following brief restriction of diet (Osborne and Mendel, 1916; Clarke and Smith, 1938; Jackson, 1936).

Much has been made of the decline in rate of wound healing with age proposed by du Noüy (1916, 1932) as a criterion of senescence. This entire theory was based on less than a dozen uncontrolled cases. Experimental studies suggest that while the mitotic rate in wounded skin is highest in infancy, little difference in cell multiplication exists between adult and senile animals, though here again the time-lag in reaching the peak mitotic rate increases with age (Howes and Harvey, 1932; Bourlière, 1950. Delayed healing of skin wounds is not clinically very evident in old people (Elman, 1953). In male mice the mitosis curve for skin *in situ* is bimodal, with peaks in infancy and again in middle age (Bullough, 1949). One easily-measured growth-system which shows a steady decline throughout later life is that controlling fingernail growth (Knobloch, 1951; Bürger, 1954).

Attempts have been made in the specific case of liver tissues to relate organ size to the existence of a mitotic inhibitor or inhibitors. Studies on plasmapheresis (Glinos and Gey, 1952) and parabiosis (Bucher, Scott and Aub, 1950) after partial hepatectomy have yielded some evidence that a humoral inhibitor, of the kind envisaged by Carrel and Ebeling (1921) disappears from circulation after hepatectomy. These observations, though interesting, could provide a suspiciously simple picture of the dynamics of growth limitation, and of consequent senescence.

An opposing view to the humoral school has been suggested

by Medawar (1942). Both in whole animals and in specific organs and tissues the rate of growth declines throughout life. Medawar points out that it is not self-evident that this decline is the result of active growth inhibition. 'We are so deeply influenced by the spirit of Newton's First Law that we tend to think that whenever a *rate* falls off, something is actively suppressing it. This is true of rates of motion, but it is not true in quite

may

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temperature approaches that of the environment. The rate at which the distribution of molecules in a closed diffusion system tends towards uniformity is likewise rapid at first, and slower and slower thereafter. In these cases, and in others similar to them, we are dealing with rates that fall off "of their own accord", with systems that tend to a certain, most-probable state at a rate which depends upon how far they have yet to go to reach it. We may look in vain for inhibitors and controllers: they are not there. I do not know whether what I have called the "kinetic picture" of growth will be found to fall within the domain of statistical mechanics. . . . It is simply a picture which we should keep in mind when thinking of growth processes, lest we should come to regard the doctrine of growth-controlling factors as self-evident; which it certainly is not.'

This argument is descriptive rather than explanatory, and the

brium state, in approaching which the cell number and growth energy vary after the manner of potential energy in the process of redistribution. The equilibrating forces, however, manifestly arise, on the evidence of explanation, from the organ's and

analysis. The decline in human population-growth is as fair a comparison. Although morphogenesis is no doubt ultimately expressible as a redistribution of energy, 'inherent' decline of rate in approaching a most-probable state is only *explanatory*, in the sense of providing a satisfactory regression of causes to the

limit of useful experiment, if 'growth energy' is itself a form of energy in the physical sense, analogous to heat in a kettle or electro-chemical energy in a battery—in the hypothetical case where a population of cells was restricted in growth by exhausting a particular energy source, employed only for growth and not for maintenance metabolism, such a system would apply, and would not only depict but 'explain' the course of events.

The great value of the approach from probability, as Medawar points out, is in preventing a facile assumption that if a growth-rate declines, this decline must result from the action of a specific toxin or inhibitor. This does not mean, however, that in a complex biological system we can avoid asking specifically *what* declines, since a decline in rate implies real quantitative and qualitative change in terms of chemical structure, and the investigation of these changes is practicable. It appears manifest that the reversion of explanted tissues to active growth is in fact caused by removal from their previous environment. It seems at least arguable whether the time lag in multiplication which characterizes aged explants is inherent in the cell at all. Simms found that the lag in cell-division of aortic explants from old fowls can be reduced by a number of non-specific procedures such as papain digestion, or washing with an ultrafiltrate of serum (Simms, 1936; Simms and Stillman, 1937). Such effects might even be purely mechanical. For most purposes it is probably also desirable to regard growth energy less as a 'store', since, to maintain the analogy, such a 'store' must be almost immediately 'replenished' after hepatectomy or explanation, than as a 'space', with walls defined by the continuously-varying properties of any individual cell in the growing tissue, and by the continuously-varying properties of the 'environment', in which are included all the adjacent cells of the same tissue. Such a concept, and, in fact, any concept of limiting size as an equilibrium process, would seem incidentally to imply the continuous replacement of any deciduous cells. The chief criticism of the humoral theories of growth limitation is their readiness to assume that the limiting factors derived from the 'environment' can (*a*) be treated in isolation and (*b*) necessarily correspond to substances rather than to physico-

chemical states and gradients. That adjacent-cell effects need not depend upon molecular hormones is well shown by Whitaker's work on the mutual orientation of *Fucus* egg cells through a simple pH gradient (see J. Needham, 1942). The search for hormonal substances which can be isolated is abundantly justifiable, but the failure to find them should not be astonishing or discouraging. There is much evidence (reviewed by Stewart and Kirk, 1954) to suggest that the 'inhibitors' detected in old serum by Carrel and his associates were nonspecific materials, probably including the serum lipoproteins. This is not to say that such materials do not exert a growth-inhibiting effect *in vivo*, or that such an effect is without physiological significance, but most existing studies certainly support Medawar's conclusion (1942) that there is no simply extractable contact hormone in adult tissue which directly restrains the growth of cells. The 'inflection' in the curve of absolute growth (weight/time) is still occasionally quoted as evidence of active growth-inhibition, but this is a mathematical fallacy which has been repeatedly exposed (Minot, 1908; Schmalhäusen, 1929; Weymouth, 1931; Medawar, 1945).

The most interesting aspect of this question, in relation to senescence rather than morphogenesis, turns once again on the supposed absence of age changes in some reptiles and fish, though speculation is vain so long as we do not know whether this absence is real. The growth of the body, and of the individual organs, in some of these forms follows much the same pattern of decline as that described by Medawar in the growth energy of isolated tissues. If reptiles whose growth declines in this way, and whose degree of histological complexity is in any case similar to that found in mammals, do not exhibit senescence, then *this* general pattern of growth-decline with age, although it occurs in many mammalian tissues treated individually, is not the 'cause' of mammalian senescence. Equilibrium cessation of growth implies the probability of one-for-one replacement in tissues which are capable of continuing division, so that unless some other process intervenes, an organism in the equilibrium state as regards growth should remain indefinitely self-maintaining, except for tissues whose degree of differentiation precludes mitotic renewal. This seems a reasonable

limit of useful experiment, if 'growth energy' is itself a form of energy in the physical sense, analogous to heat in a kettle or electro-chemical energy in a battery—in the hypothetical case where a population of cells was restricted in growth by exhausting a particular energy source, employed only for growth and not for maintenance metabolism, such a system would apply, and would not only depict but 'explain' the course of events.

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others; a genuinely morphogenetic senescence depending upon alteration of cell-responses, and having evolved, or re-evolved, within the phylogeny of vertebrates. The mammalian pattern of ageing, if it differs from that of other vertebrates, would in this case have evolved as a correlate, though not necessarily a consequence, of several fundamentally important physiological processes—homoeothermy, the development of a complex endocrine regulation centred in the pituitary, the avian-mammalian pattern of determinate growth, which is linked with this development, and the system of immune response and tissue specificity characteristic of higher vertebrates. The possible association between size-limitation and homoeothermy is interesting in view of the different relationships between pituitary and thyroid hormones in the determination of growth which have been found in mammals and in amphibians (Evans, Simpson and Pencharz, 1939; Scow and Marx, 1945; Steinmetz, 1954); at some point in vertebrate evolution, a balance-mechanism between thyroid and growth-hormone, which leads to gigantism in the thiouracil-treated tadpole, has become converted into a synergism such as normally operates in the rat or in man. Unfortunately for any phylogenetic theory, the pattern in fish appears to resemble that in mammals (Goldsmith *et al.*, 1944; Hopper, 1950). This subject will be further considered in a subsequent chapter.

6

THE MECHANISMS OF SENESCENCE

ALL theories of senescence are at present based on unwarrantable assumptions, in the absence of concrete answers to the essential questions of fact. The formulation which would receive, perhaps, the widest assent, at least in the matter of human senescence, is that morphogenetic processes lead to the differentiation of cells which have lost the capacity for division, such as neurones and skeletal muscle fibres, and to a suspension of division in others, and that processes of 'wear and tear', chemical, mechanical, or of a degree of biophysical subtlety depending on the taste of the investigator, thereafter bring about the decline of some or all of the tissues thus deprived of the power of self-renewal. This is plausible and probably true. On the other hand (1) it has been shown already that we do not know whether all vertebrates, in spite of their apparently similar degree of histological complexity, are susceptible to senescence, and there is some ground to suspect that they are not; (2) no satisfactory technique has been devised for the study of cell populations *in situ*, apart from the search for mitotic figures in sections: we do not, therefore, know the life-span of any tissue cell in its natural situation; (3) many of the descriptions of senile change in fixed postmitotics, especially neurones, are based upon the assumption that the life-span of cells specialized to this extent is limited by their incapacity for division, as appears to be the [illegible]

escence, but they cast a great deal of doubt on any assumption that the effect of wear and tear upon neurones (Bab, 1948; Vogt and Vogt, 1946) or any similar process is the prime mover

in determining the senile decline. The powers of self-renewal possessed by neurones apart from cell division have almost certainly been under- rather than over-estimated. Neurone regeneration in adult fish and amphibia can involve actual cell replacement from a reserve of neuroblasts:[1] in adult birds and mammals it is usually held to be limited to axon growth (see Clemente and Windle 1955 for a review of the large literature). Cell division, however, may not be the only means of nuclear renewal—the appearance of 'binucleate' neurones in some old animals has been taken as evidence of a process of reconstitution (Andrew 1955). Apart from this it is evident from observation that some neurones are capable of living and remaining in function for 100–150 years, unless we postulate a system of 'reserve circuits' which has so far no evidence to support it. The distinction drawn by Weismann between immortal germ cells and mortal soma still persists in many of these assumptions, in spite of the growing number of instances where differentiated somatic cells in invertebrates are thought to give rise to germ cells, or to structures having the potentialities of germ cells (Brien, 1953).

6·1 *Senescence in Cells*

6·1·1 'IRREPLACEABLE' ENZYMES

There is no self-evident reason why morphogenetic forces acting upon cells, and inhibiting their free division, should lead to their senescence. Mechanical and 'colloidal' interpretations will not do—they fail to treat postmitotic cells as the dynamic systems which they certainly are. A theory of 'mechanical ageing' in postmitotic cells could, however, be based upon the exhaustion of specific cell constituents. It is reasonable to ask how much of the senescence of such cells, if they necessarily undergo senescence, is due to the existence of 'expendable' enzymic or other intracellular structures which can be replaced only at cell division.

[1] It has even been claimed that the Purkinje cells of the mammalian

The concept of an expendable 'life ferment' appears to have originated with Bütschli (1882), although he probably regarded it simply as a material undergoing distribution from the germ cells, where it is highly concentrated, to the somatic cells in which it is increasingly diluted by subdivision. There are two essentials for our acceptance today of a system in which senescence depends on enzyme exhaustion in postmitotics—we have to postulate (1) a fixed quantity of enzyme present in the cell and exhaustible by use, and (2) the existence of an essential enzyme replaceable only at cell division. The first proviso appears already to be largely met, since it is known that the effective life-span of enzyme molecules is finite in terms of molecule-turnover (McIlwain, 1946, 1949; Theorell *et al.*, 1951).

The existence of enzyme systems renewed *only at cell division* has not, it seems, been demonstrated as such, but with the single general and large exception of 'hereditary materials', nuclear and extranuclear, it has not been sought. Some direct evidence might be derived from the action of known selective blocking agents upon bacteria of protozoa. It will be evident, however, that the idea of an 'enzyme replaced only by mitosis' falls very close to some biochemical models of the gene, which has been invested, either directly or at one remove, with direct catalytic properties. McIlwain (1946) has shown that in some catalytic systems the number of enzyme molecules per cell is of the order of unity. The inference from his figures is that if genes are not themselves molecules acting as catalysts, each gene during its 'lifetime' (i.e. between one cell division and the next) produces one such molecule. McIlwain (1949) also calculated the life-span per molecule of the nicotinic acid co-enzyme component of *Lactobacillus arabinosus* as representing the production of $5{\cdot}8 \times 10^7$ mol. lactic acid. Theorell (1951) in tracer experiments demonstrated a very slow turnover of haemoprotein enzymes, the exception being liver catalase which has a molecule/life of only 4–5 days. The wastage of such systems is due, presumably, in part to side reactions and non-specific inactivation, and in part to competitive inhibition or blocking by metabolites partially resembling the correct substrate. If the determination of such a single-molecule system were a cause of cell senescence, and if the catalyst itself were to be identified

with the gene, we would evidently need to postulate a copying mechanism at mitosis in which inactivation of the catalytic portion of the system (1) does not interfere with the production of a copy, and (2) is itself reversible: or, alternatively, one in which the products of division are two copies, not an original and a copy. It can, of course, be argued that when a differentiated cell in fact undergoes senescence, we cannot infer whether any system in it *would* be renewed by further division. Its failure to divide, even if that failure is a physiological one, leading to final differentiation, may be due to the loss of a copying mechanism. This type of problem has been encountered already, however, by workers attempting to explain some of the results of research on adaptive variation in *Neurospora* and yeasts. 'Unless gene reproduction and gene action are totally independent of each other, we have to reconcile the uniformity in the reproduction of genes with the enormous variation in what we believe to be their primary products' (Pontecorvo, 1946).

Classical genetics, although they allocate an equal proportion of nuclear genic material to every cell, have so far given little direct information about the activity of this material in cells of different kinds at any time except during mitosis, and a new category of study ('epigenetics') has had to be coined to cover this activity. Of the large number of subsidiary copying processes which have been inferred from adaptation experiments and work on anuclear portions of cells some apparently continue undiminished throughout the intermitotic period. The power of adaptive enzyme production persists in yeasts rendered non-viable by X-rays (Spiegelman, Baron and Quastler, 1951). In a neurone which may remain functioning in man for over a century, either the enzymic mechanism which maintains cell metabolism is continuously kept in repair, or it is of a kind which is almost invulnerable to incidental spoilage by use. The survival-time of non-dividing cells varies greatly, even between closely related organisms: thus in Rotifers, the life-span reaches 5 months in *Callidina* (Zelinka, 1891) and even, perhaps, several years in certain bdelloids (Murray, 1910). If 'wear' is to be invoked in these cases where senescence occurs in the presence of cellular determinancy, then the susceptibility to it must vary enormously. Other cells—squamous epithelium, for example—

have a function which depends on the progressive *change* in their structure and metabolism from formation to complete cornification. This implies a process of chemical heterauxesis within the cell, and all such 'open-ended' systems, if they continue, must eventually destroy homoeostasis. The development of histochemical methods of detecting enzymes in cells, and of selective blocking agents which irreversibly inactivate particular enzymes, already suggest experiments by which we might learn something of the limits of the postmitotic cell's power to regenerate its enzymic complement, and detect long-term changes in this power.

A special case of limited survival in the non-dividing cell is provided by the mammalian erythrocyte. This is one of the few cell-types for which a life-table can be constructed. The form of the curves obtained by a variety of methods indicates that the decay of circulating erythrocytes is a true 'senescence', i.e. that the probability of the destruction of a given cell increases markedly after it reaches a certain age. There is also, apparently, an 'infant mortality' among newly-formed red cells to make the mimicry of a metazoan survival curve even closer.

The cause of erythrocyte 'senescence' has been the subject of a good deal of study. Although it is probable that the proximate cause of erythrocyte destruction is a change in the physical properties of the stroma or the envelope of the cell, there is considerable evidence that the timing mechanism in this instance is the deleterious effect on other intracellular systems of the products of one particular oxidation-reduction system, in which methaemoglobin is formed from haemoglobin. The evidence for this view has been reviewed by Lemberg and Legge (1949). In this case we are dealing with a specialized, anuclear cell—in the nucleated avian erythrocyte, haemoglobin synthesis, and possibly other processes of renewal, continue in the circulation, but the life-span is, curiously enough, very much shorter (Hevesy and Ottesen, 1945; Hevesy, 1947) than that of the mammalian red cell.

6·1·2 CELL TURNOVER

It is necessary to point to a widespread impression among medical writers on senescence that cell turnover in the organs

of the adult animal is virtually confined to such tissues as skin, and that the 'cause' of senescence resides in the exhaustion of endocrine cells which have accompanied the individual throughout life. This may be true of some invertebrates, many of which have a wholly determinate cell-number throughout, or in certain organs, such as the corpus allatum of bees (Pflugfelder, 1948) and the suggestion cannot be refuted in terms of individual cells in man and other mammals. Such irreplaceables may exist, but the idea is in many ways open to the same criticism as that which attributes ageing to changes in biologically inert colloids, and the body of evidence suggests that it is equally erroneous. Although the rate of turnover in liver cells decreases with age, and mitotic figures become few, the mean mitosis rate in adult rats is such as to double the volume [illegible]

do not. Adrenal cortical cells are continuously replaced in the adult cat (Lobban, 1952). Mitotic activity does, however, appear to decrease with advancing age (Blumenthal, 1945; Townsend, 1946; Korenchevsky, Paris and Benjamin, 1950). The adrenals of old rats show various degenerative changes (Jayne, 1953). Mitosis varying in frequency with the sexual cycle occurs in the anterior pituitary (Hunt, 1942, 1943, 1947) though it may not affect all cell types equally, since the population changes in composition with advancing age (Parsons, 1936). *There is no direct evidence that the power of cell replacement* is lost in any endocrine gland with age, though there may be more general involutional changes at both cellular and tissue levels. The pattern of mammalian endocrine cell behaviour is predominantly one of continual division and replacement, regulated in level by hormonal influences, and often occurring in cycles. It is impossible to say at present whether there is a single key exception to this pattern, but ageing is unlikely to be so simple a matter as the defection of one type of cell. It is significant that the syndrome of senescence cannot be produced experimentally by extirpating any one gland.

The morphological changes in endocrine cells with age have

[1] I am indebted to Mr. M. Abercrombie for this figure.

been widely studied, though here, as in all pathological studies on ageing, no line can be drawn between cause and effect. Such morphological changes in pituitary cells have recently been re-examined by Weiss and Lansing (1953) and by Shanklin (1953), but without any new findings on the rate of cellular replacement. In some glandular organs, such as rat salivary glands, *mitosis becomes both rare and abnormal in pattern after the* end of active body growth, while in senile rats numerous imperfect mitoses occur (Andrew, 1953).

6·1·3 SOMATIC MUTATION

If the copying-mechanisms of somatic cells could be shown to deteriorate, like those of the *Paramecium* macronucleus, the further they travel from the germ line, senescence might result from the fact of cell turnover, not from its cessation. A possible *mechanism for this has been suggested to me by Dr. Helen* Spurway. She suggests that as a result of somatic mutation the constituent cells of some mammalian tissues may lose their autarky and become a 'community', in which both function and the capacity for replacement have undergone distribution. Such a community would contain both irreplaceable and indispensable members, and would therefore ultimately undergo senescence.

It is clear that if mammalian tissues exhibit increasingly im*perfect mitosis with increasing age, resulting in the accumula*tion of aneuploid cells, this would lead to steady deterioration of equilibrium. Any difference in liability to senescence between mammals and lower vertebrates would be explicable, in terms of this theory, on the ground that mutation rate would be higher, in all probability, with higher temperatures and chromosome numbers.

This is a highly ingenious but unproven suggestion. The contentious issue of mammalian aneuploidy generally has been *reviewed recently by Hsu and Pomerat* (1953): a large and even more contentious body of data is reviewed by Sorokina (1950). Variation in chromosome number has been reported in human (Andres and Jiv, 1936; Timonen and Therman, 1950; Therman and Timonen 1951) and pig embryos (Sorokina, 1950). In adult rat liver, Tanaka (1951, 1953) recently des-

cribed wide variation in chromosome number. He found that cells with 42 chromosomes (diploids) contribute primarily to the growth of embryonic liver and to regeneration after hepatectomy in adults, and that growth and restoration were apparently confined to diploids and subdiploids. The idea of increasingly faulty copying with increasing age, or of an accumulation of faulty copies, is one best left for verification and assessment to the cytologists, not all of whom regard the evidence for somatic aneuploidy as satisfactory. Walker and Boothroyd (1953) have shown that such 'aneuploidy' is easily simulated by faulty technique. Spurway's basic suggestion should, however, be susceptible to verification. Clearly any evidence that the copying of somatic cells deteriorates is of gerontological importance, and would, if established, restore the relevance to metazoan ageing of much which was formerly written concerning the senescence of clones.

6 1 4 SPECIFICITY

Campbell and Work (1953) have recently drawn attention to the significance of the fact that animals cannot in general be immunized against their own proteins; and they suggest that the action of the genotype in determining specificity may be chiefly a negative one, in the prevention rather than the creation of a specific configuration. It is a matter of extreme interest that the character of the proteins produced by the animal body appears to change with age, as judged by calcium binding power (Lansing, *et al.* 1949 Hansard *et al.* 1954, serological properties (Duran-Reynals, 1940) and amino-acid composition (Lansing *et al.*, 1951) and by the appearance of collagen and elastic fibres in skin (Ejiri, 1936; Gross and Schmidt, 1948, 1950). The acid-extractable collagen decreases markedly with age (Banfield, 1952). In general these products arise, however, not from aged cells, but from the cells of aged organisms, and the change in specificity has taken place over several cellular generations. It has occasionally been suggested that senescence is a manifestation of an 'immune' response to endogenous hormones (e.g. Picado and Rotter, 1936; Freud and Uyldert, 1947). A more subtle change in specificity of cell response, or of the properties of cellular products, whether it be

interpreted immunologically, or, more probably, morphogenetically, cannot be ruled out. If cells in general or certain cells could be shown to acquire adaptive resistance to physiological regulators, as do bacteria to unfamiliar metabolites, from generation to generation, interesting possibilities would certainly be opened.

Connection between the processes of senescence and those of immunology was suggested long since by Metchnikoff, though in rather a different context (1907). He attributed the senile atrophy of differentiated tissues, especially neurones, to overactive phagocytosis, brought on by constant exposure to the toxic (and antigenic) products of symbiotic and endoparasitic bacteria: the second part of this theory has received more publicity than the first. Metchnikoff was also responsible for the suggestion that many morphogenetic processes in the embryo are 'immunological' in character, within the wide definition of immunology implied in his theory of phagocytosis, and that the defence mechanisms of the adult animal are directly derived from mechanisms which, in embryonic life, have been primarily concerned with morphogenesis. The embryo is not exposed as a rule to exogenous antigens, though its own chemical composition is changing. More recent work, in fact, has shown that exposure to an antigen during embryonic life can lead to a lifelong inability to react against that antigen (Billingham, Brent and Medawar, 1953). The possibility that morphogenetic mechanisms give rise in ontogeny to the defence mechanisms of the adult, which is evidently true in the case of some mechanisms of chemical homoeostasis, is still popular in Russian research. Whether such effects modify cell responses during the later phase of development, senescence, is unknown.

Gaillard (1942) has carried out a long series of studies relating the degree of differentiation which can be produced and maintained in tissue explants to the age-status of the press juice in which they are grown. According to these results, functional differentiation in endocrine and other explants can be obtained if they are grown successively in press juices from embryos of increasing age, while some degree of regression of structure occurs if the series is reversed, and explants are grown in juices of decreasing age-order. This process has not so far been followed

into senescence. No doubt if explants could be cultivated in media exactly simulating the chemical and physical environment and its changes through all the stages of development, they would pass through all the normal phases of *in vivo* histology. The point of interest to the gerontologist is to know how far it is possible to maintain a *status quo* at any point. Analysis of the power of tissues to mark time developmentally while retaining function requires more elaborate methods of organ and tissue culture than are so far available, but the lead given by Carrel in applying these techniques to age-processes has hardly been pursued with the vigour it merits. Gey (1952) has recently referred to the *in vitro* culture of 'thyroid, parathyroid, adrenal cells, and the germinal epithelium of the ovary' even to the production of follicles, but these findings remain contentious.

6·2 *Endocrine Senescence*

6 2 1 GENERAL

The early discoverers of hormones were fully convinced that they had in their hands the key to the prevention of senescence in man. The fact that little of their enthusiasm persists today is due very largely to the manner in which the confluence of two deeply emotive subjects—ageing and the gonad—affected scientific judgement in the early years of the century. The hypotheses of the rejuvenators were in many respects reasonable, if their published claims were not. In any discussion of endocrine senescence it is probably worth restating (1) that organ and tissue grafting are appropriate and fully respectable techniques for the investigation of senile change, and that they have given misleading answers chiefly because the wrong questions were asked, (2) that the use of hormones in the palliation of senile changes in man, although it is largely ineffective, was a reasonable experiment which has not yet been exhausted, and (3) although gonadal 'senescence' does not 'cause' somatic senescence (this was self-evident in antiquity, from the life histories

Characteristic variations in hormone output occur throughout the mammalian life cycle; they are of two types—cyclical and secular. These changes are the biochemical equivalent of the sudden movements of embryonic tissue which are seen in speeded-up films of developing organisms—they are part cause, part effect, and they represent only the outward and visible manifestation of changes in the quality and quantity of cell response. The hormones most likely to be linked directly with the senile process, such as the growth hormone of the pituitary, cannot be estimated in the intact animal. Of those which can be so estimated, the group of 17-keto-steroids show a decline which continues with the rise of the force of mortality (McGavack, 1951; Kirk, 1949; Hamburger, 1948; Robinson, 1948; Hamilton and Hamilton, 1948; Hamilton, Hamilton and Mestler, 1954 (Fig. 41)). The concept of an 'adrenopause' analogous to the menopause seems to have little to support it at present. Apart from this, there is no single hormonal change which correlates with senescence, no single endocrine organ, of those which can be removed without fatal results, whose extirpation produces the syndrome of senility in mammals; *and no hormone or combination of hormones* which is known to produce more than a limited, and apparently secondary, reversal of senile changes. Ablation of a gland is not the same thing as its senescence *in situ*, and in surgical castration for prostatic and mammary cancer there is evidence that interconversion may take place between adrenal and gonadal steroids, but no simple hypothesis that senescence is a 'withdrawal' effect is substantiated by the existing experimental evidence. It appears that the sequence of developmental changes in endocrine activity which ends in senescence cannot so far be made to run backwards by hormone supplements, except in a very minor degree.

In a long series of studies, Korenchevsky (e.g. Korenchevsky and Jones, 1947, 1948; Korenchevsky, Paris and Benjamin, 1950, 1953) has tried to show how far hormone supplements can reverse the senile process, judged by the restoration of the relative hypoplasia of organs. A great many of the senile structural changes described in endocrines are closely paralleled, though at a lesser level of severity, by the changes in structure

which follow gonadectomy, and many of them are reversible by gonadal hormones. (Korenchevsky *et al.*, 1950; McGavack, 1951). The peripheral effects of sex hormones in senility, such as the recornification of the vagina by oestrogen (Loeb, 1944), are familiar enough. The decrease of mitotic rate and degree of vacuolation in the adrenal (Townsend, 1946; Blumenthal, 1945) and the increase of collagen and reticulum in the capsule

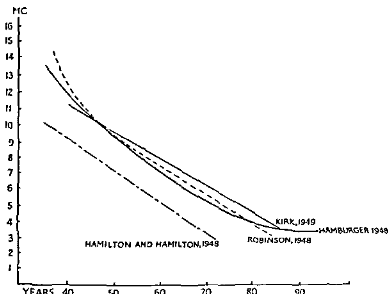


Fig. 41.—Neutral 17-Ketosteroids, 24-hour urinary excretion (Kirk 1949).

and in the parenchyma (Dribben and Wolfe, 1947) which occur with advancing age are partially reversible by oestrogen, and more fully reversible by a combination of oestrogen, androgen and progesterone (Korenchevsky, Paris and Benjamin, 1950). In the pituitary of the senile rat, Wolfe (1943) found a decrease in eosinophils, but no increase in basophils vacuolation, like that which follows castration, occurred in the basophils with increasing age. These changes, particularly the decrease in eosinophils, are at least partially reversed by testosterone propionate (Wolfe, 1941). The senescent changes in

fowl pituitary described by Payne (1949, 1952) were greatly hastened by gonadectomy. In other words, gonadal failure may contribute to senescence, but probably does so only when it occurs at a certain point in the endocrine developmental programme.

In some instances, direct estimations of the capacity of senile endocrines to respond to physiological stimuli have been made. Solomon and Shock (1950) tested the response of the adrenal cortex in 27 young and 26 old men to a dose of adrenocorticotropic hormone (ACTH) and in 15 young and 13 old men to a dose of 0·4 mg adrenaline. No difference in eosinopenia was observed after ACTH, but adrenaline produced a significantly greater eosinophil depression in the young group. From this it was inferred that the senile cortex can still secrete 11–17 oxysteroids without gross impairment, but that the response of the pituitary to acute adrenaline stimulation is lower in old than young subjects. Pincus (1950) likewise found no impairment of response to ACTH in old men compared with young controls. But with chromatographic techniques, Rubin, Dorfman and Pincus (1955) have examined the range of α-17 ketosteroids produced at different ages. There is here little difference between men and women: in both, the greatest decline with age is in androsterone and aetiocholan-3α-ol-17-one, and the second greatest in the 5α-11-oxygenated steroids. Such studies offer considerable promise.

The hypophysis is clearly the site of election for 'fundamental' and all-explaining endocrine changes leading to senescence—the part which it has played in the provision of such emotionally-satisfying theories follows naturally from the fact that it is known or credibly suspected to be involved in the regulation of almost all mammalian processes of homoeostasis. Its proximity to the hypothalamus enables it to be linked with theories which locate senescence in the central nervous system. Hypophysial factors in senescence have also a special importance because of the relation of the hypophysis to the control of growth. In its simplest form, starting from cellular exhaustion, the idea of a primary pituitary senescence drew plausible anatomical arguments from the histological studies of Parsons (1936) and Simmonds (1914) on long series of glands from subjects of various

ages, or from more recent work such as that of Payne (1949, 1952) on the ageing fowl.

If there has been a tendency for the existence of the pituitary gland to serve as a pretext for vagueness of thought concerning the nature of senescence in mammals—the function formerly discharged by the pineal in the search for the seat of the soul—there are also solid arguments for its direct involvement, certainly as mediator, but possibly also as originator, of senile processes. Because the pituitary is profoundly concerned with several processes of homoeostasis, and is involved with morphogenetic timing mechanisms like that which initiates puberty, it is easy to develop hypotheses of pituitary senescence which do not depend upon an unbiological argument in terms of single hormones.

The function of trophic hormones appears to be the provision of one limb of a system of negative feedback, by which the level of effector-

senescence

equilibriun

can be induced in a model control system, normally dependent upon negative feedback, by several types of change.

Consider a system in which a device A produces a signal which increases the activity of a second device B, and in which, at the same time, the activity of B produces a signal which reduces the activity of device A. The properties of most self-regulating biological systems can be reproduced in this model by varying the characteristic of the stimulus A → B or the negative feedback B → A, and the number of stable states of A or B. If there is no time-lag in either of these processes, the level of output B will tend to be constant and self-restoring. If there is an appreciable time-constant in one limb of the circuit, the system will tend to function as a relaxation oscillator. In

recover, and this represents one whole cycle. It is a requisite for the functioning of such a system that the unmodified output of A shall tend to increase in the absence of output B, i.e. that

the state of A is inherently unstable. If output A be assumed to be the pituitary gonadotrophin and output B the gonadal hormone, then the immediate response of the pituitary to castration, or senile decline in gonadal response, is of the unstable type, though other mechanisms operate later to restore regulation. Where, as may be the case in the male, the pituitary-gonad balance operates as a level-control, gradual failure of B's response would be expected to cause a gradual increase in output A. In a similar system containing a time-constant, and therefore behaving cyclically, blocking would be expected to occur at one point in one particular cycle, with a proportionately greater rise in output A.

The importance of this homoeostatic concept is that in the simplified model self-regulating equilibrium can be turned to progressive disequilibrium by several types of change. Decline in the capacity of either A or B to respond to B → A or A → B will result in a permanently unstable state of A. If the response of A fails, B will also be driven into maximum output. Decline in the capacity of B to produce B → A will induce the unstable state of A. Decline in the capacity of A to produce A → B will lead to the relapse of B into its stable state of zero output. This, however, where B's output effects other systems, will cause disequilibrium in a complex physiology. In addition to these purely quantitative changes, biological cybernetic mechanisms are also capable of exhibiting, and, in development, characteristically do exhibit, qualitative change in the specificity both of signal and response, which further complicates the picture.

Although analogies from circuits oversimplifying the reality of mammalian homoeostasis, they indicate the number of variables to be considered in studying the senescence of homoeostatic systems; and they indicate some of the ways in which such senescence can be analysed. Evidence suggests that in the case of the gonad it is the function of B which declines. With the pituitary trophic hormones, other than the gonadotrophins and ACTH, *in vivo* estimation of levels, corresponding to the measurement of output A, cannot as a rule be carried out. The action of these homoeostatic systems, moreover, is not expressed through static components but through a developing organism

in which long-term trends in cell specificity are themselves controlled by the signals involved in the homoeostatic process—as if the system A ⇌ B were fitted in a vehicle whose movement it controlled, but which travelled into a hotter and hotter environment, thereby upsetting the characteristics of A and *B*.

These highly complex hormonal homoeostatic systems are of the greatest importance in higher vertebrates, although the problem of 'three-dimensional' homoeostasis, or homoeostasis superimposed on morphogenesis, is general in all developmental physiology. The views of Minot (1908) upon 'cytomorphosis' (differentiation and maturation) as a cause of senescence carry the very important, and at first sight very probable, inference that no complex organism, and certainly no vertebrate, can remain in an indefinitely stable equilibrium. Where growth processes and differentiation are superimposed on homoeostasis they are analogous to 'drift' in a control system—on this basis any system of differential growth must tend to increasing disequilibrium, unless the developmental 'drift' itself modifies the homoeostatic system to keep them appropriate to the altered situation.

6·2·2 GONAD-PITUITARY SYSTEM

Senescence of the *gonad* regularly precedes or accompanies senescence of the owner in a number of phyla—so much so that declining reproductive capacity is a token of senescence almost as valuable as the direct measurement of increased force of mortality. The relation of gonadal senescence to somatic senescence has clearly much evolutionary interest, since once the first is complete, in an organism, to the point at which that organism's contribution to posterity is no longer statistically significant, any further adverse change in viability is generally speaking inaccessible to the influence of natural selection, except in a very roundabout way.

In almost all litter-bearing mammals, a decline in litter size is characteristic of senescence. The long post-reproductive period found in women is exceptional in mammals. It probably represents a genuine biological difference, quite apart from the far greater perfection of the techniques for keeping human beings

alive. Compared with the more gradual disappearance of ova in other mammals, the human menopause is unusually complete and sudden. The range of this phenomenon among primates is not at present known. Nobody has seen a postmenopausal monkey (Krohn 1955).

There is some cause for regarding gonadal senescence and the group of effects which follow senile gonadal withdrawal as a separate 'senescence' from that of the animal as a whole, since gonadal supplements can reverse a whole series of subsidiary senile changes without materially reversing the progress of somatic senescence judged by survival. In the castrated male mammal, gonadal hormone supplements may perhaps actually shorten life. There is no demonstrable androgen deficiency in normal senile male rats (Korenchevsky, Paris and Benjamin, 1953), nor, probably, in most old men.

Although sex hormones do not rejuvenate the organism in the manner envisaged by writers such as Voronoff, they produce a closer approach to 'rejuvenation', covering more structures and body processes, than do any other hormones which have been investigated. In addition to their effects upon the secondary sexual characters, such as beard growth (Chieffi, 1949) or structure of vaginal epithelium (Loeb, 1944; Allen and Masters, 1948) and upon the genitalia themselves, androgens (Kenyon, 1942; Kochakian and Murlin, 1931; Kochakian, 1937) and probably also oestrogens (Kenyon, 1942) exert an important 'anabolic' effect with nitrogen retention and increased protein synthesis, and produce a number of unexpected peripheral changes, generally in the direction of a restoration of 'young' structure (Korenchevsky, Paris and Benjamin, 1953). Thus oestrogens have been stated to produce a striking reversal of the atrophy of the senile nasal mucosa (Kountz, 1950) and certainly produce extensive changes in senile skin, with dermal regeneration (Goldzieher and Goldzieher, 1950; Chieffi, 1950a) and restoration of elasticity (Chieffi, 1951). That the possibility of 'rejuvenation by replacement' is limited, even where the reproductive organs are concerned, is shown by Kirk's failure (1948, 1949) to restore the phosphatase activity of senile prostatic secretion with androgens, although this activity is so restored in young hypogonadal males.

The relation of these changes and their reversal to the general picture of senescence in mammals remains extremely obscure. Of the more general processes in which gonadal hormone withdrawal plays a part, few have been identified with certainty. It has been suggested, for instance, that the osteoporosis of old age is a result of the withdrawal of gonadal anabolic hormones (Allbright, 1947). All theories of gonadal action in senescence have, however, to accommodate the probability that *in mammals senile change in the force of mortality of apparently typical form, and at approximately the typical specific age, occurs in both sexes in the absence of both gonads*, regardless of the age at which these are removed.

The mechanisms which fix the timing of puberty, and of the human menopause, are the most obvious of all mammalian age processes, and quite the most promising experimentally. The key problem is to determine whether the timing-factors reside primarily in the gonadal cells or elsewhere. The application of transplantation techniques to this question has been reviewed by Krohn (1955). Unfortunately, it already appears likely that there are considerable interspecific differences. The ability of the gonadal cells *in situ* to respond to gonadotrophin has sometimes been regarded as controlling the onset of puberty. Pituitary gonadotrophin is detectable in the hypophysis of the 17 cm. pig foetus (Smith and Dortzbach, 1929) and the implantation of glands from 3-month-old rabbits is as effective in inducing puberty as implantation of adult glands (Saxton and Greene, 1939). The ovaries of immature rabbits do not respond to injected gonadotrophin (Hertz and Hisaw 1943, Parkes 1942–44, Adams 1953) On the other hand, it has long been known that when ovaries are transplanted reciprocally between young and old animals, it is the age of the recipient before or after puberty, not that of the ovary, which determines function or non-function (Foà, 1900, 1901; Long and Evans, 1922) and in some species gonadotrophin readily induces precocious ovarian and testicular development. Domm (1934) was able to induce crowing at 9 days of age and treading at 13 days in cockerel chicks by injections of pituitary gonadotrophins. The timing-mechanism is stable within a species or a genetic strain. Human puberty very exceptionally occurs during childhood without any obvious pathological cause ('constitutional

precocious puberty'—Novak, 1944) and pregnancy has actually been reported in a child of five (Escomel, 1939). In albino rats, according to Mandl and Zuckerman (1952) genetic factors seem to play the major part in determining the age of puberty. Lorenz and Lerner (1946) likewise found clear evidence that age of sexual maturation in turkeys is heritable. 'The reactivity of the gonads may be the most important factor in determining the time at which sexual maturity actually occurs, but the factors which affect this reactivity are largely unknown' (Robson, 1947). Change also takes place at puberty in the specificity of pituitary response—while oestradiol induces pituitary and adrenal hypertrophy in rats castrated after puberty, it reduces pituitary and adrenal weight in animals castrated while still immature (Selye and Albert, 1942).

The end of the reproductive period, as well as the beginning, is marked by changes in gonadal reactivity. These have led some writers to regard the human menopause as a form of depletion-senescence (Swyer, 1954): Hertig (1944) describes the exhaustion of a 'capital' of ova, which is not increased during post-natal life, but his findings suggest that the actual menopause precedes the end of all follicular activity. In man and many other mammals (the only admitted exceptions occur in Lemuroidea, the galago and the loris), the occurrence of oogenesis during post-pubertal life has been doubted—the case against it has been persuasively put by Zuckerman (1951): this 'perennial controversy' has been continued by Parkes and Smith (1953), who found evidence of oocyte regeneration in rat ovaries grafted after freezing. But it is in any case most unlikely on existing evidence that the menopause occurs *because* the supply of ova is exhausted. Engle (1944) mentions the finding of apparently normal corpora lutea in women of 50: at the menopause most if not all ova and follicles have normally disappeared. Kurzrok and Smith (1938) found that in the human ovary, in contrast to the senile ovary of some other mammals, ova cease to be found, and that this change occurs at or soon after the menopause. They consider that the postmenopausal ovary can no longer respond to pituitary gonadotrophin. Gardner (1952) transplanted ovaries between old and young rats, and apparently found a greater tendency to malignant

change in old ovaries carried by young hosts. Details of this study have not yet appeared.

In rats semicastrated during old age, Wiesner (1932) found a marked reduction in compensatory hypertrophy of the remaining ovary. One major feature of senescence is probably progressive reduction of the ovarian reserve in terms of hormone production. Such an effect, rather than the consumption of ova, may account for the earlier menopause in semicastration (Masters, 1952). Failure of the ovary to respond to pituitary stimulation is almost certainly the proximate cause of the human menopause. (See also Klebanow and Hegnauer, 1949.)

In rare instances a failure of the menopause itself has been reported—menstruation is said to have persisted in a woman of 104 (Novak, 1921)—but pathological causes were probably responsible for some at least of these cases.

By far the most interesting fact from the standpoint of senescence is the striking increase in pituitary gonadotrophin level at the human menopause, and the comparable but more gradual increase in senile men (Henderson and Rowlands, 1938) and rats (Lauson, Golden and Severinghaus, 1939). This not only indicates a change in gonadal tissue reactivity with age, but it also shows how limited senile processes may provoke compensatory reactions and further disturb homoeostasis. Ovariectomy in certain strains of mice predisposes them to carcinoma of the adrenal cortex, which can be prevented by oestrogens (Woolley and Little, 1946). The senile increase in gonadotrophin closely resembles that which follows castration, though it develops more gradually (in female rats—Lauson, Golden and Severinghaus, 1939). Witschi (1952) found that in women the castrate level of FSH by pituitary gland assay is established very rapidly after the menopause, and persists for the rest of life, while in men the rise is far more gradual, the castrate level being reached only at 70 years and only by a few individuals. In a majority of cases the hypophyseal FSH content either remains at the normal adult level or falls, occasionally even below childhood levels. But in male eunuchs castrated in childhood, pituitary gonadotrophin output may remain, from the time of normal puberty into middle age, at about ten times the normal level (Hamilton, Catchpole and Hawke, 1944, 1945).

There is no evidence that this staggering increase, maintained *over 40–50 years, has any observable effect on the rate of ageing.*

623 HORMONAL REGULATION OF GROWTH IN VERTEBRATES

In mammals, where growth and differentiation are difficult to dissociate experimentally, we have abundant evidence of senescence even in the longest-lived forms. In amphibia, where there is a clear-cut metamorphosis, and where growth and differentiation can be manipulated with relative ease, we have so far no evidence of senescence. We cannot directly find out whether the life of intact amphibia, the neoteny of the axolotl, or the gigantism of athyroid tadpoles, ends in senescence, for the practical reason that axolotls may well be capable of living for 50, and normal frogs for twelve, fifteen or twenty years. This conspiracy of circumstances perpetually recurs in the study of ageing. The large literature of lower vertebrate endocrinology and morphogenesis cannot be brought to bear on the problem, for lack of actuarial data.

Both homoeotherms and poikilotherms, whether they metamorphose or not, tend to pass through an earlier phase of active growth and a later phase of active reproduction, each characterized by a separate type of endocrine control, and the second by a relative loss of regenerative in favour of reproductive capacity. These phases are separated by the operation of a timing-mechanism which is linked to processes in the juvenile phase. In mammals, these phases are apparently controlled by the pituitary growth and gonad-regulating mechanisms successively. In lower vertebrates the differentiation-process and the transition to adult function appears to depend on a pituitary-thyroid balance. Pituitary growth hormone of mammalian origin is able to promote the growth of fish (Swift, 1954).

The relation between morphogenesis under the influence of gonadal hormones and loss of regenerative power has special interest in gerontology. Grobstein (1947) found that when the gonopodium of poeciliid fish differentiates, under the influence of androgens, regenerative power is lost: he stresses the analogy between this process and the loss of regenerative capacity in the developing anuran limb. Such a change need not depend upon irreversible loss of cellular capacity to grow—this does

not appear to be the case in amphibian limbs (Borssuk, 1935; Polcžaiev and Ginsburg, 1939) but the physiological loss of repair-power may be as complete, so far as the intact animal [illegible]

hormonal influences which affect protein anabolism, and regulate growth in mammals, especially in man. Where these factors have been studied, they give little support to the idea of a simple relation between senescence and growth-cessation, and even less to the conception of a single, 'master', endocrine inhibitor which can be detached from the general pattern of progressing developmental change. The pattern which exists in man has all the complication of a dynamic system where homoeostasis coexists with change. Much of the existing information is provisional, and there are as yet no studies extending into the period of senescence. It is plain, however, that in man, and probably in some but not all other mammals, the 'anabolic' stimulus to form new protein is not the same throughout life. In adult life it is closely linked to the gonadal cycle. The extent of the differences in endocrine control of growth between determinate growers such as man and continual growers such as the rat has not yet been mapped, and very little is known of the hormonal control of growth in lower vertebrates. The existing evidence is quite enough, however, to render any static conception of growth-cessation in terms of single-hormone deficiencies untenable. A more accurate picture would perhaps be obtained by treating pre-pubertal and pubertal life as separate instars separated by what amounts to a biochemical metamorphosis.

The growth of human beings, like that of *Daphnia* (p. 93), occurs in two overlapping cycles—one prepuberal, the other coinciding with puberty. (See Figs. 42, 43.) The prepuberal cycle has its most active phase during the first six months of life. This cycle, according to Kinsell (1953), is almost wholly controlled by the pituitary growth hormone. The puberal cycle appears to be evoked directly by anabolic steroid hormones derived from the gonad and adrenal cortex. During both cycles

a minimum output of thyroid hormone is required to maintain growth and development. At puberty, in response to the pituitary gonadotrophins, the gonads produce steroid hormones which directly stimulate the growth of bone and of soft tissues.

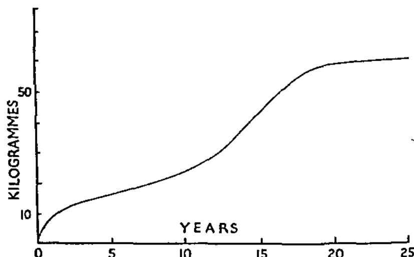


FIG. 42.—The postnatal growth in weight of male children (kg/years) (from the data of Quetelet).

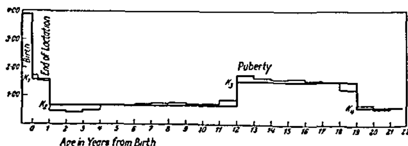


FIG. 43.—Annual growth increment in boys, from the data of Quetelet k_1-k_4 = growth constants at each period (from Schmalhausen, 1928).

The process of bone growth in man is, however, self-limited, since the same hormones produce skeletal maturation and fusion of the epiphyses. There is reason to suspect that they also inhibit the production of pituitary growth hormone—

probably through a negative feedback system from the level of protein anabolism. It is particularly interesting to notice that acromegalic symptoms (McCullagh and Renshaw, 1934) or frank gigantism (Joedicke, 1919) are occasional sequels to castration in males—so, however, are polyuria and diabetes insipidus (Hamilton, 1948). The puberal growth phase in girls appears to be largely of adrenal origin, since the growth-promoting effects of oestrogens and of progesterone are less marked, except in the promotion of Ca and PO_4 retention, than those of androgens (Kinsell, 1953). It is generally held that thyroxin potentiates the action of pituitary growth hormone in mammals (Evans, Simpson and Pencharz, 1939; Scow and Marx, 1945) during the prepuberal phase, as well as hastening differentiation. This does not appear to be the case in anurans, where thiouracil produces pseudogigantism, and a balance between thyroid and pituitary has been postulated (Steinmetz, 1954), one evoking differentiation and the other growth and a 'juvenile' condition.

This picture, which requires considerable amplification, accords reasonably well with the known effects of various endocrine deficiencies in producing dwarfism or gigantism in man. To some extent the [illegible] of the puberal cycle curtails the [illegible]

administration of growth hormone (Freud, Levie and Kroon, 1939), as they are in natural gigantism. On the other hand, abolition of the whole gonadal influence by prepuberal castration has, at least, no gross effect on the life-span. Here again the analogy to Edlén's findings in *Daphnia* is remarkably close.

Various workers have suggested that mammalian senescence 'is' (or involves) the decline of growth hormone production, and that it 'is' (or involves) the long-term effect of the pituitary gonadotrophin on non-gonadal tissues. Insofar as senescence results from differentiation, this is doubtless true, but the experimental question is rather this—to what extent can the administration of one or more 'anabolic' hormones affect the power of continued homoeostasis in adult animals? It is possible that the growth hormone itself may be the 'juvenile hormone' of the

mammalian pre-imaginal period. It is a primary stimulator of protein anabolism and somatic growth. The change from a protein-building and nitrogen-retaining economy, and the negative specific acceleration of growth, are two of the most evident correlates of senescence (Mayer, 1949). The administration of growth hormone 'confers strangely youthful proportions on the nitrogen, fat and water components of the body, even in old animals' (Asling *et al.*, 1952). Change in specificity of tissue response to growth hormone certainly *appears* to occur in some mammals, and this change coincides with the attainment of maturity and the appearance of a fresh anabolism-maintaining mechanism. The experimental work of Young in England and Li in America suggests that before a critical time, injected growth hormone induces only protein anabolism—after that time, it also induces diabetes. This is the pattern in man, the kitten (Cotes, Reid and Young, 1949) and the dog (Campbell *et al.*, 1950) but not in the rat (Bennett, Li and Evans, 1948) or, apparently, the mouse (Moon *et al.*, 1952) which respond by continued growth. That the change in specificity involves endogenous as well as exogenous hormone is evident from the occurrence of diabetes in association with spontaneous acromegaly. Evidence for the existence of a separate diabetogenic principle is not very impressive (Raben and Westermeyer, 1952; Young, 1953). Complete ablation of the anterior lobe in adults leads to failure of growth but not, in general, to other acceptable evidences of senility (in rats) though this cannot be shown from the life-table.

In experimental studies, even highly purified growth hormone administered to rats produces decreasing effects upon nitrogen retention and upon growth after repeated administration (Whitney *et al.*, 1948). These experiments, however, have invariably been carried out with heterologous (usually ox) hormones, and, as in the case of antigonadotrophic effects, no physiological importance can be attached to the apparent increase in tissue resistance.

Of the other hormones concerned in growth and differentiation, the pituitary thyreotropic hormone appears in most mammals which have been studied (rats—Turner and Cupps, 1938; rabbits—Bergman and Turner, 1941; mice—Adams and

Mothes, 1945; cattle—Reece and Turner, 1937) to reach a peak at or about puberty, with a subsequent decline which has never been followed by assay into old age. The decline of general metabolism with increasing age, which has been frequently linked with the decline of growth-capacity as an index of 'physiological ageing', appears to involve both a fall in thyroid activity and perhaps a decline in cell response, since thyroidectomized rats show no senile decline in heart rate and O_2 uptake, and old normal rats are decreasingly responsive to thyroxin administration (Grad, 1953). The declining heat-production of ageing human subjects may well be a reflection as much of muscle atrophy as of thyroid involution.

The results obtained by McCay, using dietary restriction, could be regarded as the consequences of dietary hypophysectomy. Such a state of affairs interferes with the production of both growth hormone and gonadotrophin, and its effect is a general slowing of the 'integrating system' of growth + development. The separation of these systems in mammals is a problem of great interest and considerable practical difficulty. Dietary retardation greatly postpones, but cannot be kept at such a level as to prevent, the onset of oestrus (Asdell and Crowell, 1935). McCay, Sperling and Barnes (1943) found that the capacity of retarded rats to resume growth was ultimately lost if retardation was prolonged. Apparently if growth is delayed without differentiation, it may ultimately encounter a block at the cellular level.

[illegible] problem of selective inter-

sectomy in 6-day-old rats does not arrest the eruption of teeth or the opening of the eyes, but later sexual and pre-sexual development is suppressed. Untreated animals ultimately die from paralysis due to cerebral compression, the brain outgrowing the cranium. Rats which survive the postoperative period have been maintained in good health by growth hormone supplements. In these supplemented rats, the rate of growth was only slightly less than that of unoperated controls. Skeletal development was normal, but adult organ-differentiation and sexual maturation did not take place. Three such 'metathetelic'

individuals, were kept for 200–300 days in an attempt to produce gigantism. The end results of this experiment have not yet been reported in full. It would be interesting to know how long such animals are capable of living, and what senile changes they ultimately exhibit.

Selective suppression of gonadotrophin production is not yet feasible, though recent studies with *Lithospermum* extracts suggest that the chemical 'dissection' of pituitary effects with chemical antagonists is not, perhaps, an unreasonable hope (Wiesner and Yudkin, 1952). The effect upon life-span of inducing precocious puberty in mammals does not appear to have been studied: mice, which mature very early, are not ideal subjects, and an experiment on longer-lived mammals encounters the familiar practical difficulties.

7

CONCLUSION

We have now briefly examined some of the evidence which requires to be considered, and some of the questions which require to be answered, in attempting to understand animal senescence. We have seen, in particular, that many organisms appear to have been provided by evolutionary selection with a 'programme' of development and function which is directional and finite, and that progressive loss of the power to remain in stable function occurs towards the end of that programme. Weismann suggested that senescence is itself a functionally-determined item in the programme: it seems more probable that as the contribution of successive age groups to the next generation of progeny is reduced by natural causes, so the selection-pressure declines, and the efficiency of the homoeostatic mechanisms with it. The organism ultimately dies of old age because it is now an unstable system which is provided with no further sequence of operational instructions, and in which divergent processes are no longer co-ordinated to maintain function.

In some cases the system fails suddenly, at a fixed point, after the pattern of the senescence of rotifers or red blood corpuscles. Some such cases apparently depend on the existence of cell constituents renewable only by division. In mammals the decline of resistance and the rise of the force of mortality are gradual and smooth, and agree well with the probable shape of a curve representing the declining efficiency of the evolutionary pressure towards survival at different ages.

Insofar as any general theory of senescence is justified, this seems at present the most plausible. It is probably as unprofitable to discuss the 'cause' of ageing as to discuss the 'cause' of

development. Senescence is a change in the behaviour of the organism with age, which leads to a decreased power of survival and adjustment. It is not a single overall process, except in the evolutionary sense which we have outlined. Various factors in varying proportions contribute to the senile change in different species. Among these are the deterioration of irreplaceable structures; the sum of previous injuries which are imperfectly repaired; and progressive morphogenetic changes in the nature and specificity of cell response and organ function. Any or all of these factors may contribute to senescence in a given species. Experimental removal of the factor which operates earliest in the life-span may reveal another subsequent to it, and so on. There is no conclusive evidence to incriminate cessation of growth as a 'cause' of senescence, except in cases where cell division ceases altogether. Senescence is not an 'inherent' property of the metazoa, but one which they have on several occasions acquired as a potentiality, probably through the operation of evolutionary forces directed to other biological ends. In this respect the senescence of insects and of man is probably a comparable process only to the same extent that the eyes of these organisms are comparable structures. It is obvious that such a conception, while it does not prevent us from ascertaining what factors produce the age-deterioration in a given species, excludes general physiopathological theories of the 'causation' of ageing as a whole.

Unlike the functional evolution of the eye, senescence is typically an undirected process—not a part of the programme, but a weakening of the directive force of the programme, an escape from co-ordination, combined with the arrears of processes which once contributed to fitness but are now running free. Attempts to invest the programme of morphogenesis with metaphysical or supra-natural properties (Driesch, 1941; Bürger, 1954) have already been adequately answered by J. Needham (1942), and need not be dealt with here. The idea of senescence as the 'fated' or 'destined' end of the organism, i.e. a positively-subsistent and ordered process of life-curtailment, though it is not always the fruit of an avowed vitalism, has much in common with it. Such treatment of senescence as an evolved entity, and the idea that it must have developed as a

positive character, has almost certainly gained plausibility, like so much else in the biological literature of old age, from human preoccupations. The gerontologist, with the prolongation of human life in mind, is interested in something which is not, as such, of interest to the evolutionary 'demon', and whose evolution is in no sense comparable with the evolution of sight. Senescence has no function—it is the subversion of function. On the other hand, as Huxley (1942) suggests, the evolutionary process in man has been transferred in the process of cephalization from the 'demon' to the operation of conscious intellect. It should now be possible in our thinking to separate human goals from the effects of selection, and to renounce the animistic confusion between them which has influenced the past theoreticians of old age. The whole conception of 'senescence', in fact, belongs to the field of applied science. It embraces a group of deteriorative effects which we have isolated because they are deteriorative—in other words, because human beings dislike them. Some biological thinkers have reduced themselves to impotence in this field by the cultivation of philosophic doubt whether senescence is an 'entity' at all. Viewed abstractly it is not, any more than disease is an 'entity', but the same biologists

of keeping human beings alive in active health for a longer time than would normally be the case—in other words, to prolong individual life. People now rightly look to 'science' to provide the practical realization of perennial human wishes which our ancestors have failed to realize by magic—or at least to investigate the prospect of realizing them. Under the influence of the study which is necessary to fulfil such wishes, the character of the wish itself generally changes in the direction of realism, so that most people today would incline to prefer the prospect of longevity, which may be realizable, to a physical immortality which is not, and, *pari passu*, 'potentielle Unsterblichkeit' is al-

aggressive restatement from gerontologists, particularly at a time when there are scientists who seek ethical reasons why human life ought not to be prolonged, at least in communities of which they are not themselves members. Although it has much fundamental interest, we have seen that senescence is not biologically speaking a very satisfactory entity. It appears in most animals only under artificial conditions, and it would probably seem to most of us pointless to devote great effort to so arbitrary a part of development if it were not involved with a primary human desire. As it is, medicine has always accepted the prolongation of active and healthy human life in time as one of its self-evident objects, and this object has only been seriously challenged in the past two decades by the growth of pathological forms of anti-liberalism. Gerontology differs from other fields of medical biology only in the fact that while most medical research is directed to making the curve of human survival as nearly as possible rectangular, gerontology is directed to prolonging the rectangle, and shifting the point of decline further in time from the origin. The applied character of such work, and the object it has in mind, would not require emphasis or defence at a period of culture when they ran no risk of provoking a neo-Malthusian uproar. The beggarly opinions of such writers as W. Vogt (1949) merit the rebuke of James Parkinson (1755–1824), that 'if the population exceeded the means of support, the fault lay not in Nature, but in the ability of Politicians to discover some latent defect in the laws respecting the division and appropriation of property'. Postponement of old age, like all the other advances in human control of environment, must involve corresponding social adjustments: in the prevention of presenile mortality, as the graphs in Fig. 3 abundantly indicate, social, economic and political factors clearly predominate already. But whatever problems might be raised by future increases in the human specific age, in this and other fields medicine can afford to treat protests based upon an interested misreading of the biology of human societies with the contempt they deserve, as a compound of illiberal opinions and bad science. The emotional preoccupation of former workers with magical rejuvenation did no good to the progress of science, but it was at least a humane preoccupation.

In fact, the social correlates of longevity, which are probably its most important practical aspects, have been omitted altogether from consideration in this book. It is clear throughout phylogeny that there is a relation between survival into the senile period and the existence of a social mode of life. In some cases longevity has evolved as a prerequisite of social organization, in others social organization itself increases the possibility of survival into old age, while the social group very probably draws adaptive benefits from the existence of old individuals. Both these trends appear to be at work in social primates. The potential life-span in palaeolithic man probably resembled our own: its realization has been possible through the development of a complex social and rational behaviour. While therefore it is legitimate to abstract the idea of an evolutionary programme in morphogenetic or physiological terms when we discuss the development and senescence of an individual man or of a worker bee, in neither case is this 'programme' really detachable from the social programme which coexists with it, and which plays an equally important part in the determination of selection or survival. The irrelevance of discussing the biology of *individual* animals, even of non-social species, divorced from their ecology, has long been evident. Prolongation of the social activity and significance of the individual human being almost certainly leads to a change in the shape of the life-table, others things being equal. Continuance of active work, retention of interests, of the respect of our fellows, and of a sense of significance in the common life of the species, apparently make us live longer, lack of these things makes us die young. This is a

compulsory psychological and social 'winding-up' imposed on the human individual by our form of society and our norms for the behaviour of old people we do not yet know, but it is certainly a very considerable part, and the most important measures for the prolonging of useful individual life which come within the range of the immediately practicable are all concerned with social adjustment. The contrast between the place of the (relatively few) aged in primitive societies (Simmonds, 1945, 1946) and the relatively many in our own (Sheldon, 1949;

Sanderson, 1949) is particularly striking. In primitive cultures '*important means of security for old people are their active* association with others and assistance in their interests and enterprises. They are regarded as repositories of knowledge, imparters of valuable information, and mediators between their fellows and the fearful supernatural powers . . . The proportion of the old who remain active, productive, and essential in primitive societies is much *higher than in advanced civilization*, for they succeed to an amazing degree in providing cultural conditions which utilize the services of their few old people' (Simmonds, 1946). How little this applies to our own culture is evident from the studies of Sheldon (1949); other evidence suggests that although in certain groups (Lehman, 1943), such as amateur naturalists—or among those who retain, perhaps, some of the magico-social functions of the primitive elder (politicians, judges and clergy) the element of social support based upon continued activity leads to an apparently superior retention of the capacity for public life, the society of compulsory retirement, individual privacy and the small family has little to offer to old people. This is a topic which cannot be pursued here, but its importance in the social medicine of age is paramount at present.

The problem of medical gerontology at the biological level, however, is to prolong the human life cycle in time, either by deformation and stretching or by addition, and in particular to prolong that part of it which contains the period of 'adult vigour'. Such a problem could theoretically be solved in any of three ways, bearing in mind the evidence regarding the existence of a developmental 'programme'—that programme could be prolonged by the provision of new developmental operations; or its movement, throughout or in part, could be slowed down; or active life could be maintained after the expiry of the programme by piecemeal adjustment of homoestatic mechanisms with supplements, medicaments and prostheses of various kinds.

The first of these possibilities, though it is biologically the most interesting, does not merit discussion at present, at any rate in relation to man. We do not know enough about morphogenesis to interfere with it clinically, except in a few simple deficiency states, let alone devise and apply a sequence of self-

regulating operations in growth or development subsequent to normal adulthood. The third possibility is that which is already, and very justifiably, receiving the major part of the energy devoted to clinical studies upon human ageing. The removal of successive causes of death should in theory increase the specific age. It is interesting to notice that there is so far very little evidence of such an effect. It was once widely believed that with the removal of 'pathological' causes of death the specific age would rise very rapidly in man and approach the recorded maximum. Although research on the diseases of later life has not yet had time to reach a stature comparable with the life-saving powers of surgery and epidemiology in early life, it seems possible that even with increased control over neoplasms and cardiovascular disease the age at death might only come to be more and more normally distributed about the present specific age. Most people who die in old age are found at post-mortem to have several further pathological processes at work, beside the one from which they died. If an arbitrary normal distribution of deaths due to 'pure' senescence were assumed, the shape of the curve could be inferred from the shape of that one-half of the existing, positively-skew curve which lies between the ages of 75 and 100. Such an assumption may well, however, be false. The smoothness of the curve between those ages is largely due to manipulation by actuaries, relying on a conventional end to the human survival curve to help them over statistically insignificant material (Freudenberg, 1949). We have not reached the limits of the purely prosthetic and supportive treatment of senility, and we are unlikely to do so for a very long time.

There remains the possibility of prolonging life by slowing down the movement of the developmental programme. Such slowing, to be of medical interest, must be compatible with retention of normal vigour and activity. The mere duration of individual existence could quite possibly be extended, as John Hunter proposed, by some form of artificial hibernation, punctuated by periods of activity: but this possibility is more interes [illegible] and perhaps politicians than t[illegible] to be [illegible]

in later life. The prolongation of that part of the life cycle which lies normally between the eighteenth and fiftieth years of age, even by a small percentage, would come nearest to fulfilling our objectives. The prolongation of childhood presents special interest, since, on existing mammalian evidence, it is quite probably feasible by relatively simple, if heroic, means such as calorie-restriction. Such a prolongation would have interesting and far-reaching social consequences, both upon the family and upon the acquisition of skills: its effects on character-structure would be even more interesting. It seems very probable that the time-scale of prepubertal development in the majority of mammals is relatively labile. There is so far no direct evidence that the same applies to later stages in the life cycle. Dietary restriction, although it may favour longevity, does not greatly delay senescence in adult mammals, and it may be that the time scale of the adult period, after somatic growth has ceased, is not susceptible to any major interference without at the same time destroying normal function. To assess the possibilities of such interference we require to know how far 'marking time' at each stage of the mammalian developmental programme is possible, and, if possible, is compatible with functional health. It is also a matter of practical import whether the rate of child growth influences the length of the period of adult vigour in man (Sinclair, 1955). The degree of linkage between growth, development, and metabolism may vary considerably at different periods of the life cycle, and the bulk of the work upon their separation has been carried out only in non-mammalian embryos and larvae. We have to reckon with the possibility that the post-pubertal mammal behaves like an imago—that its life-span is closely linked to metabolism, which, in homoeotherms, is virtually invariable by the methods which can affect it in invertebrates, and that the fundamental change which leads to eventual senescence has already taken place at puberty. In this case, interference with the length of the adult phase could only be prosthetic.

There remains the possibility that a substantial change in the specific age, and in the duration of healthy life, might result from *one particular* adjustment. This was the hope which led to the use of sex hormones for purposes of 'rejuvenation', and

which was largely disappointed. If such an adjustment is possible, it is most likely, perhaps, to concern one or more of the anabolism-promoting substances which maintain growth in the young animal.

To the question 'Can the effective human life-span be prolonged artificially?' the most probable answer, based on all these possibilities, would appear to be 'Yes'. To the further question 'By what factor?' no meaningful answer can be given until we know more of the nature of the predominant processes which determine human senescence. Supplementary questions dealing with the degree of reversibility in established senile change cannot at present be answered at all, beyond the conjecture that the morphogenetic programme in man is hardly likely to be simply reversible in any fundamental sense, but that the irreversibility of local changes in ageing is at present probably over- rather than under-estimated.

The only excuse for such speculation is, in any case, the possibility that it will drive us into the laboratory to ascertain the facts and to answer the questions it raises, thereby removing gerontology from the field of 'entelechies' and 'inherent principles' into that of intelligible evidence.

In planning research upon a subject such as senescence, it pays to put to ourselves the questions which most urgently require to be answered, and then to select from the list in the likely order of practicability. From the defects which exist in the evidence, the essential preliminary questions concerning senescence which we must ask appear to be these.

(1) Does senescence occur in all vertebrates?

(2) In what instances, if any, among vertebrates does senescence coexist with continuing somatic growth, or non-senescence with fixed size?

(3) To what extent is arrest of developmental processes compatible, at different stages of vertebrate ontogeny between conception and senility, with activity and normal function? Is the retardation of further development, towards senility, realizable *after* puberty in mammals?

(4) To what extent is the artificial induction of somatic growth possible in the mature vertebrate, and what is its effect on the specific age?

(5) What are the limits of the power of enzyme-renewal and physicochemical self-maintenance in fixed post-mitotic cells?

(6) In the case of single organs such as the mammalian ovary, how far is the expectation of life of the organ intrinsic in its stage of development, and what is its life-span in passage through successive young hosts? What, in more general terms, is the relation between the physiological age of individual tissues and the chronological age of the host animal?

I have singled out these specific questions for attention as being rather unlikely to be solved *incidentally*, in the course of general biological research upon other topics. The great bulk of the information which is missing on other specific points is likely to be derived eventually from studies in endocrinology or morphogenetics which are not undertaken *ad hoc*; this type of background research cannot be hurried on, ahead of the general progress of knowledge, except by the cultivation of interest in ageing among biologists of all kinds.

Three main types of research are involved in the investigation of our six preliminary questions—study of the phylogeny of senescence in vertebrates, study of the correlations and the experimental modification of growth and development in populations where the life-span can be concurrently measured, and study of tissue-environment relationships through the creation of age chimaeras. The problems of the first of these studies have already been mentioned. A reliable test of 'senescence' which correlates with the decline of resistance, does not *kill* the individual animal, and can be related to actuarial senescence by an intelligible process of reasoning, might offer some solution. The development of such a test would probably depend, however, upon the establishment of the part which declining growth-energy plays in the process of ageing. The time-lag in explant growth might conceivably give a basis for some such attempt. Any method of marking tissue cells *in situ*, to enable their life-span to be determined like that of red blood corpuscles, would be a highly desirable advance, and a key to many doors. The study of growth and development relations, and the whole group of studies which require to be undertaken in determining

the factors which predominate in mammalian ageing, or which can modify it, encounter a rather different obstacle. The choice of experimental animals for such work obviously presents great difficulty, since it is necessary either to work on forms whose life-span is short compared with that of the investigator, or to use elderly individuals whose early history has not been followed. The complication which this time-factor introduces is of great importance for the planning of research. Man is by far the most numerous senile animal, and his life cycle is extremely well known—even to the point at which we can estimate his physiological age by inspection; some research on senile men can be justified ethically, but the gerontological aspects of laboratory animal-breeding cannot much longer be neglected, since in many problems no further progress is possible until mammals of known life cycle, heredity and physiology are available in quantity. At present the choice lies between experiment on patients, the basing of general conclusions upon the behaviour of invertebrates and small rodents, and postponing investigation for several years while a chosen population of larger mammals completes its life cycle. Failure to deal with the logistics of this problem now will hinder research in ten or twenty years time, and that hindrance could be avoided by forethought.

Another extremely important source of information is likely to be found in the creation of *age chimaeras*. In spite of the well-merited disrepute incurred by much work upon organ grafting in relation to old age, the resources of modern transplantation techniques now offer a very tempting range of experimental possibilities. The reimplantation of stored infant tissues into the same animal, the cross-transplantation of organs such as ovaries, or tissues such as portions of skin, and the observation of the reciprocal influences of host and implant, are technically practicable and established procedures. Parabiosis between animals of disparate age but identical genotype, or even between retarded and unretarded littermates, is another tool of the same kind. The emphasis of such research is likely to be chiefly directed to dissecting tissue and somatic factors in the senile process, but its possible use in experimental, and even later in clinical, prosthetics is thoroughly well-justified. This is, of

course, not the first occasion in biology when a procedure which was attempted with enthusiasm and abandoned in disgust has come back into useful currency after a period of meditation and study. An equally productive field may well be that of organ culture, initiated by Carrel, but still comparatively little used.

Apart from such specialized investigations, serious progress depends on the cultivation of general awareness among biologists of the importance of prolonging their study of every animal into the senile period, of collecting and publishing life-tables, especially for cold-blooded vertebrates under good laboratory conditions, and of seeking confirmatory evidence of the distribution of senescence in phylogeny. A few years of propaganda to zoologists in training might bring in a rich factual harvest later. Much modern research into ageing tends to be desultory, although the single subjects with which it deals are important in themselves. We ought to try to devise critical experiments, and if we destroy more hypotheses than we demonstrate, this is a subject which can well stand such treatment in contrast to the speculation which has gone before. The most desirable condition for progress in gerontology at the moment is that the exact nature and scope of the problems raised by senescence should be understood, and the possibility of new experimental evidence borne in mind, during the planning and assessment of all biological research, even when it is primarily directed to other objects. Senescence, like Mount Everest, challenges our ingenuity by the fact that it is there, and the focusing of our attention on it is unlikely to be fruitless.

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